

THE INVESTIGATION OF FACTORS
INFLUENCING THE STEREOCHEMISTRY
OF THE WITTIG REACTION

By
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A DISSERTATION PRESENTED TO THE GRADUATE COUNCIL OF
THE UNIVERSITY OF FLORIDA
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE
DEGREE OF DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA
December, 1965

ACKNOWLEDGMENTS

The author wishes to express his appreciation to his research director, Dr. George B. Butler, for his guidance and encouragement during the execution of this work.

The author also expresses his gratitude to his fellow graduate students and associates for their helpful suggestions and criticisms.

Particular thanks are due Mrs. Frances Kost and Mrs. Thyra Johnston for their conscientious typing of this dissertation.

The author also thanks his wife for her patience, encouragement and understanding. Without her cooperation this work would not have been possible.

The financial support of the Petroleum Research Fund is also gratefully acknowledged.

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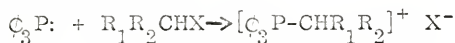
CHAPTER I

INTRODUCTION

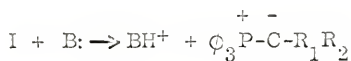
Historical Background

Since Wittig and Geissler¹ first reported the olefin synthesis which has become known as the Wittig synthesis literally hundreds of papers have been published concerning the synthetic and mechanistic aspects of the reaction.

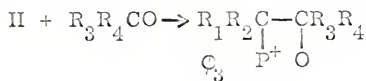
This synthesis in its general form involves the reaction of a phosphorane derived from a phosphonium salt with an aldehyde or ketone. The phosphonium salts are usually prepared from triphenylphosphine and an alkyl or arylalkyl halide. The phosphorane is produced from the phosphonium salt by removal of an α -hydrogen by a suitable base. Addition of a carbonyl containing compound to a solution of the phosphorane forms an intermediate betaine which then collapses to produce the olefin and triphenylphosphine oxide.



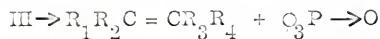
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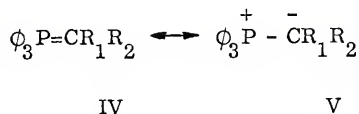
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Although the reaction appears straightforward synthetically, mechanistically the reaction is exceedingly complex. The structure of the phosphorane is apparently a resonance hybrid of canonical forms IV and V. Form IV is also referred to as an ylene and form V as an ylide. Form IV requires the assumption of $d\pi$ bonding,



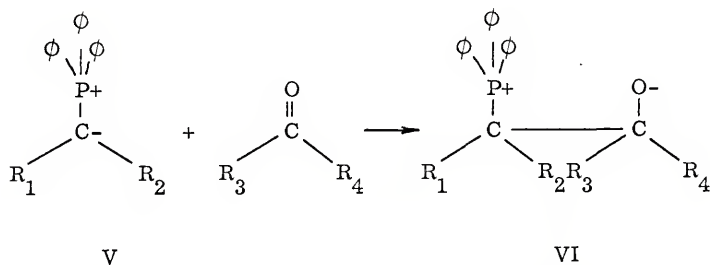
between carbon and phosphorus. That such bonding exists for phosphorus and other elements of the third period has been demonstrated² by base catalyzed a deuterium exchange studies. Form V is that of a carbanion, the extremely strong conjugate base of the phosphonium salt.

If we assume that structures IV and V approximate the limiting forms of a phosphorane we can see that the degree to which this structure resembles either IV or V will be dependent on the nature of the substituents on phosphorus and carbon. Jaffe³ has calculated that one of the criteria for $d\pi$ bonding is the existence of a positive charge on phosphorus in its singly bonded structure. It follows that groups on phosphorus which would be electron donating, e.g. alkyl groups would lessen the importance of the contribution of form IV to the hybrid. Likewise the incorporation of electron withdrawing groups on carbon, e.g. carbethoxy would tend to make form IV more important. Regarding the reactivity of the phosphorane we find that groups increasing the contribution of form IV to the hybrid produce a less reactive species. This can be seen in comparing the properties of triphenylfluorenylidene phosphorane⁴ and tributylethylidenephosphorane. The former contains groups capable of delocalizing the charge on the carbon and intensifying the positive charge on the phosphorus.

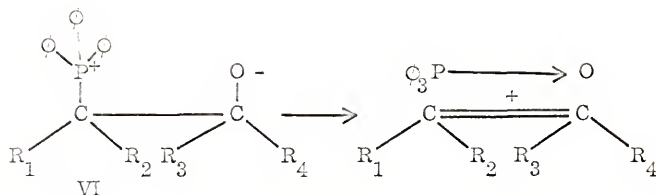
It is extremely unreactive. It can only be hydrolyzed by refluxing with strong base. The latter compound contains groups which tend to diminish the positive charge on phosphorus and increase the carbanion character of the structure. It is hydrolyzed rapidly on exposure to the atmosphere. Both compounds will react with carbonyl compounds but the conditions for carrying out the reaction are much more vigorous for the fluorenylidene phosphorane.

Between these two extremes lie almost a continuum of compounds with varying reactivities. It is this range of reactivity which has made the study of the Wittig reaction both interesting and challenging. Work done on one system cannot be directly correlated with a more or less reactive system. This is especially true of the stereochemistry of the reaction.

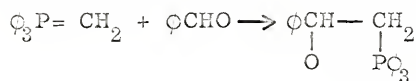
The mechanism of the reaction as postulated by Wittig⁵ involves an attack by form V of the phosphorane on the electrophilic carbon of the carbonyl to give a betaine.



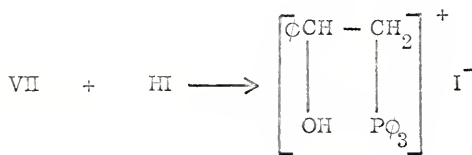
The betaine then may collapse via a four membered cyclic transition state to olefin and triphenylphosphine oxide. In attempting to elucidate the mechanism Wittig⁶ studied the reaction between methylenetriphenylphosphorane and benzalde-



hyde. During the reaction Wittig was able to trap the betaine by the addition of hydrogen iodide giving 2-phenyl-2-hydroxyethyltriphenylphosphonium iodide which



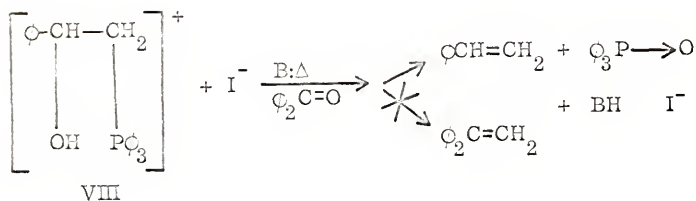
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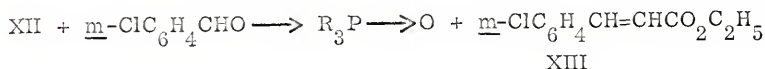
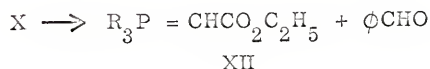
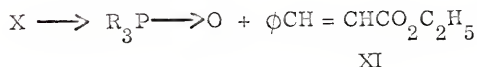
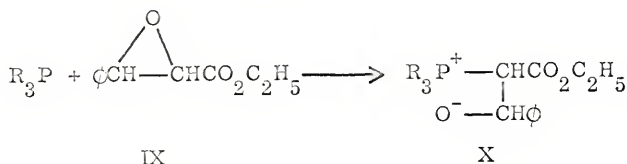
VIII

on heating gave styrene and $\text{C}_3\text{P} \longrightarrow \text{O}$. He also refluxed benzophenone with the betaine hydroiodide, but was unable to obtain 1,1-diphenylethylene, the product one might expect if betaine formation were reversible. Wittig therefore concluded that betaine formation is irreversible.

However, Filszar, Hudson and Salvadori⁷ found that the lithium bromide--ether complex of the betaine isolated by Wittig yielded no olefin products on heating but rather benzaldehyde. These workers concluded that betaine formation is reversible and that decomposition of betaine to olefin and phosphine oxide is rate determining.



Speziale and Bissing⁸ have demonstrated the reversibility of betaine formation by reacting triphenyl and tributylphosphine with cis and trans-ethyl phenylglycidate in the presence of meta-chlorobenzaldehyde.



They found using a 1:1:1 molar ratio of triphenylphosphine: trans-ethyl phenylglycidate: meta-chlorobenzaldehyde that they obtained 48.7 per cent cis ethyl cinnamate; 17.4 per cent trans ethyl cinnamate; 3.0 per cent cis meta-chlorocinnamate and 30.9 per cent trans meta-chlorocinnamate.

These workers further showed through a kinetic study of the reaction between a series of substituted benzaldehydes with carbomethoxymethylenetriphenylphosphorane (a stable ylide) that the rate of reaction is second order, first order in

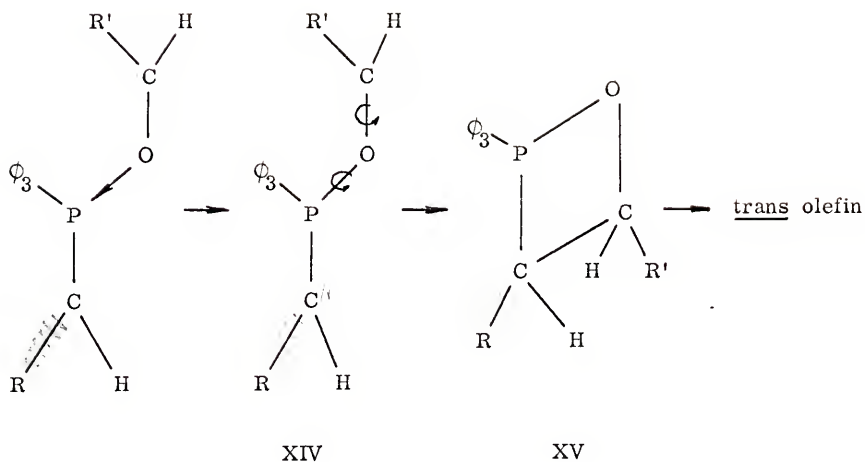
ylide and first order in aldehyde. They found that the reaction rate is increased by increases in solvent polarity, substitution of butyl for phenyl on the phosphorus of the ylide and by electron withdrawing substituents on the aldehyde.

The mechanism they postulated based on kinetics and the epoxide ring opening reactions mentioned previously is slow, reversible betaine formation followed by rapid decomposition of the betaine to olefin and phosphine oxide.

House and Rasmusson⁹ had previously suggested a mechanism for the reaction of acetaldehyde with carbomethoxymethylenetriphenylphosphorane to give methyl tiglate and methyl angelate in which there is a rapid reversible formation of betaines with slow preferential decompositions of the stereoisomeric betaines to products.

Concerning reactive ylides, Wittig, Weizmann and Schlosser⁶ had observed that though betaine formation with reactive ylides is rapid, taking place within a few minutes, the decomposition of betaine requires standing at room temperature or heating for several hours. They concluded that betaine decomposition is the slow step in this type of reaction.

Bergelson and Shemyakin¹⁰ interpreted the stereochemistry observed in the reaction of stable ylides (giving mostly trans olefin) as opposed to unstable or reactive ylides (giving mostly cis olefin) by using two different reaction paths. For reactions involving stable ylides they believed that because of the decreased electron density about the carbon attached to the phosphorus of the ylide, attack would take place by the carbonyl oxygen on the phosphorus rather than by the carbanion of the ylide on the carbonyl carbon.



This would be followed by rotation either about the phosphorus-oxygen or carbon-oxygen bonds to give the more stable (trans) betaine which would then decompose to olefin and phosphine-oxide. This mechanism involves irreversible betaine formation in direct conflict with the results of Speziale and Bissing.⁸

Reactions of reactive ylides would take place by the accepted path involving attack of the carbanion on the carbonyl carbon.

Trippett¹¹ recently discussed the work of Speziale and Bissing and his own results in contrasting the kinetics and mechanism involving stable and reactive phosphoranes. Since stable phosphoranes produce intermediate betaines which cannot be isolated Trippett proposes a potential energy diagram in which the "valley" representing the betaine is quite shallow. He believes that the transition states T_1 leading to the betaines from reactants and T_2 leading from the betaines to products

resemble the structures of the betaines more than they resemble either the products or reactants.

Using these assumptions and a relative rate equation based on them he concludes that the most important factor in determining the ratio of isomers in the reaction of stable ylides is the relative rate of betaine formation with smaller

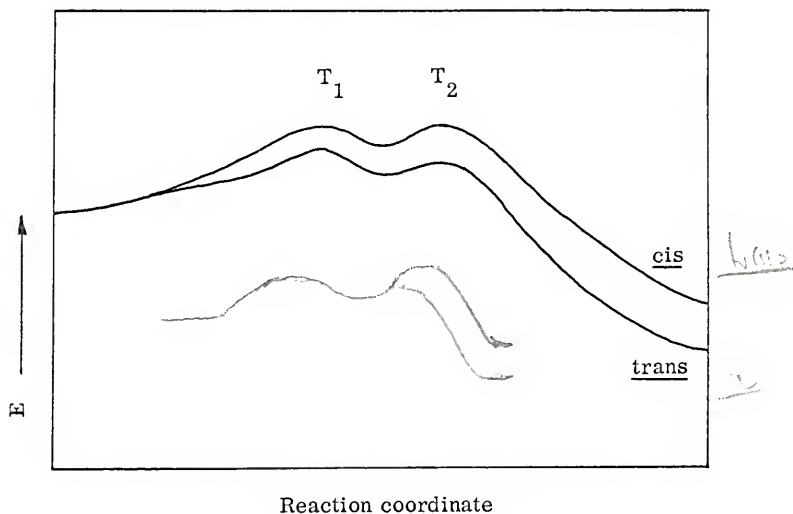


Figure 1. Energy Profile for the Reaction of a Stable Ylide

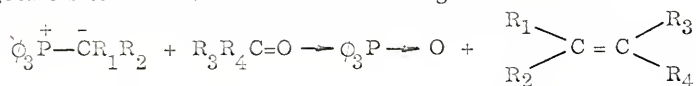
contributions from the relative rate of betaine dissociation and decomposition all acting in the same direction.

For the case of very reactive phosphoranes, e.g., $\text{CH}_2=\text{P}-\phi_3$, he maintained that betaine formation is still reversible but now the difference lies in the isomeric betaines. The one giving cis olefin dissociates faster than it decomposes to

products and the one giving trans olefin decomposes to products faster than it dissociates.

Stereochemistry

Although we have already touched on the stereochemistry of the Wittig reaction in our discussion of the mechanism considerably more work has been done on this phase of the synthesis. If one starts with an aldehyde or an unsymmetrical ketone and an unsymmetrical phosphorane the olefin resulting can exist in either of two geometrical forms. The olefins receiving most attention



have been those in which either R_1 or R_2 is H and R_3 or R_4 is H. Wittig and Schollkopf⁵ in some early work observed that the reaction between benzaldehyde and benzylidenetriphenylphosphorane give cis and trans stilbene in a 30:70 ratio respectively, whereas the reaction of benzaldehyde with allylidenetriphenylphosphorane give cis and trans 1-phenylbutadiene in a 45:55 ratio respectively.

Ketcham¹² and coworkers conducted a reaction between p-nitrophenylmethylenetriphenylphosphorane and anisaldehyde and p-methoxyphenylmethylenetriphenylphosphorane and p-nitrobenzaldehyde. The product mixture in the former reaction consisted of all trans olefin, while in the latter reaction the product contained 48 per cent cis and 52 per cent trans olefin. They reasoned that the less reactive p-nitro ylide reacts reversibly with the unreactive anisaldehyde while the reactive p-methoxy ylide reacts irreversibly with the very reactive p-nitrobenzaldehyde giving an almost statistically controlled product mixture.

Speziale and Ratts¹³ also found that they obtained all trans olefin from p-nitro-benzaldehyde and the stable ylide carbethoxychloromethylenetriphenylphosphorane.

Wailes¹⁴ however reported that the reaction of dodecylidenetriphenylphosphorane (a reactive ylide) and propynal give after treatment with ethylmagnesium bromide and carbon dioxide the enynoic acid containing 80 per cent cis isomer.

Truscheit¹⁵ and coworkers using butylidenephosphorane and 12-acetoxy-dodec-2-enal obtained 70 per cent of the cis diolefin. Using ethylidenephosphorane they obtained 67 per cent cis diolefin.

Kucherov¹⁶ et al. using the stable carbethoxymethylenetriphenylphosphorane and 2,4,6-octatriene-1,8-diol obtained a 57 per cent yield of all trans olefin. They also obtained all trans olefin using the same aldehyde and 3-carbethoxyallylidene-triphenylphosphorane.

There are in the literature many more references concerning the stereochemistry of the Wittig reaction but like most of those above they have not been either intensively or extensively studied. However, there appeared in the last three years several stereochemical studies of the reactions which deserve attention.

Shemyakin and Bergelson^{10,17,18,19} in a series of papers have published an abundance of useful, though sometimes controversial information concerning the chemistry of moderately unstable ylides. The system used in their early experiments was the reaction of propionaldehyde with benzylidenetriphenylphosphorane to give phosphine oxide and β -ethylstyrene.

Using a series of solvents they obtained the results shown in Table 1. Their explanation of the isomer ratios involves a solvent-ylide complex which may be considered either a coordination compound or a solvate. Whatever its exact nature they say that this complex produces a "mutual inaccessibility of the phosphorus and oxygen

TABLE 1
SOLVENT AND HALIDE ION EFFECTS

| Solvent | Added Salt | β -ethylstyrene | |
|----------------------|------------|-----------------------|---------|
| | | % cis | % trans |
| Benzene | -- | 26 | 74 |
| Benzene | LiCl | 20 | 80 |
| Benzene | LiBr | 27 | 73 |
| Benzene | LiI | 41 | 59 |
| Dimethylformamide* | -- | 65 | 35 |
| Dimethylformamide* | LiCl | 73 | 27 |
| Dimethylformamide* | LiBr | 71 | 29 |
| Dimethylformamide* | LiI | 74 | 26 |
| Ethyl Ether | -- | 31 | 69 |
| Tetra-hydrofuran | -- | 33 | 67 |
| Ethanol* | -- | 47 | 53 |
| Aniline | -- | 51 | 49 |
| <u>n</u> -Butylamine | -- | 43 | 57 |
| Diethylamine | -- | 32 | 68 |
| Triethylamine | -- | 24 | 76 |
| Piperidine | -- | 36 | 64 |

* Base = $\text{CH}_3\text{CH}_2\text{O}^-$

in the prereaction complex" and that "under such conditions the betaine" (leading to the cis olefin) "forms more readily than its diastereoisomer."¹⁰ The order of the effects noted in the solvent they relate in the case of the oxygen containing compounds to relative nucleophilicity while in the amine series they feel steric factors are of particular importance. Dimethylformamide, they believe, though weakly basic, possibly interacts with the phosphorus of the ylide through its strongly polarized oxygen rather than its nitrogen.

These workers also found that the addition of lithium halides to the reaction in benzene and DMF gives increased yields of the cis isomer as shown in Table 2.

The rationalization of these effects again involves a halide complex with the positively charged phosphorus of the ylide. This diminishes its electrophilicity thus favoring the formation of the betaine leading to the cis isomer "due to electrostatic repulsion between the halide and oxygen electronic shells. The selective formation of cis olefins shows that this effect is considerable."¹⁰

In their later papers Shemyakin and Bergelson have clarified their reasoning on the interactions leading to the stereochemistry of the Wittig reaction in the presence of Lewis bases. They propose coordination of the Lewis base with the phosphorus which is facilitated by a transition of the phosphorus from a tetrahedral to a trigonal bipyramidal configuration in which the three phenyl substituents become coplanar. They predict that as a result of repulsion between the electronic clouds of the phosphorus and oxygen the betaine leading to the trans olefin is "destabilized by steric repulsion of the skewed R and R' substituents" thus leading to predominant cis olefin. They point out, however, that though this might be the case with some systems it does not prevail in all. Considering the case in which betaines

TABLE 2
COMBINATION EFFECTS ON STEREOCHEMISTRY

| Ylide | Aldehyde | Solvent | Salt | Ylide:RCHO | % Yield | Cis:Trans |
|--|------------------|-------------------|------|------------|---------|-----------|
| $\text{EtCH}=\text{P}\phi_3$ | ϕCHO | Dimethylformamide | LiCl | 1:1 | 52 | 73:27 |
| $\text{EtCH}=\text{P}\phi_3$ | ϕCHO | Ethyl Ether | LiCl | 1:1 | 70 | 80:20 |
| $\text{EtCH}=\text{P}\phi_3$ | ϕCHO | Ethyl Ether | LiH | 1:1 | 46 | 22:78 |
| $\text{EtCH}=\text{P}\phi_3$ | ϕCHO | Benzene | LiCl | 1:1 | 62 | 79:21 |
| $\text{EtCH}=\text{P}\phi_3$ | ϕCHO | Benzene | LiH | 1:1 | 33 | 35:65 |
| $\text{EtCH}=\text{P}\phi_3$ | ϕCHO | Benzene | LiH | 2:1 | 55 | 65:35 |
| $\text{EtCH}=\text{P}\phi_3$ | ϕCHO | Benzene | LiH | 1:2 | 28 | 59:41 |
| $\text{EtCH}=\text{P}\phi_3$ | EtCHO | Dimethylformamide | LiCl | 1:1 | -- | 95:5 |
| $\text{EtCH}=\text{P}\phi_3$ | EtCHO | Dimethylformamide | LiBr | 1:1 | -- | 95:5 |
| $\text{EtCH}=\text{P}\phi_3$ | EtCHO | Dimethylformamide | LiH | 1:1 | -- | 95:5 |
| $\text{EtCH}=\text{CHCH}=\text{P}\phi_3$ | EtCHO | Dimethylformamide | NaBr | -- | 43 | 28:72 |
| $\text{EtCH}=\text{CHCH}=\text{P}\phi_3$ | EtCHO | Isopentane | LiBr | -- | 52 | 23:77 |
| $\text{EtCH}=\text{CHCH}=\text{P}\phi_3$ | EtCHO | Isopentane | LiCl | -- | 67 | 14:86 |
| $\phi\text{CH}=\text{P}\phi_3$ | ϕCHO | Dimethylformamide | -- | -- | -- | 75:25 |
| $\phi\text{CH}=\text{P}\phi_3$ | ϕCHO | Ethyl Ether | -- | -- | -- | 30:70 |

are formed faster than they decompose, they reason that now the steric course of the reaction "depends on the relative energies of the stereoisomeric betaines not only in the most stable conformation, but also in the eclipsed reacting conformation closely allied to the four-membered transition state. If the reacting betaine conformations are sufficiently well differentiated energetically, the over-all equilibrium will be shifted in the direction of the betaine that most readily decomposes into olefin and phosphinoyl. This can lead to stereoselectivity, even when the diastereoisomeric betaines in the most stable conformation differ little in energy." In the case of the reaction of benzylidenetriphenylphosphorane with propionaldehyde in benzene which gives 80 per cent trans- β -ethylstyrene they state that the selectivity illustrated here is hard to explain on the basis of the small differences in non-bonded interactions observed in the two betaines. They believe that a more important factor in this case is the stabilization of the incipient double bond by the phenyl group which would only be possible in the betaine leading to the trans olefin.

They¹⁹ also consider the possibility of steric control by changing the concentration of reactants, thereby reducing the reversible dissociation of the betaines. While equimolar amounts of ethylidenetriphenylphosphorane and benzaldehyde in benzene in the presence of lithium iodide give 34 per cent cis- β -ethylstyrene the doubling of either the aldehyde or ylide concentration practically doubles the amount of cis isomer found.

In another group¹⁸ of experiments these investigators demonstrated that substantial amounts of trans olefin could be obtained from moderately unstable ylides contrary to the usual experience. For example, using propionaldehyde and 3-ethylallylidenetriphenylphosphorane they obtained the results shown in Table 2.

House and Rasmusson⁹ investigated the reaction between acetaldehyde and 1-carbomethoxyethylidenetriphenylphosphorane and between ethylidenetriphenylphosphorane and ethyl pyruvate to give mixtures of methyl angelate and methyl tiglate. They found that the reaction between the stable phosphorane gave 96.5 per cent trans ester whereas the unstable phosphorane gave 68 per cent trans ester. They rationalized these results by postulating an equilibrium in the formation of betaines and more rapid decomposition of the betaine leading to the trans ester because of increased stabilization in the transition state. This increased stabilization could arise because only in the trans betaines would the carbomethoxy group be able to become planar with the incipient double bond. In the cis betaine coplanarity of the carbomethoxy group would be prevented by interference with the adjacent methyl group. The increased amount of trans isomer obtained with the ethylidenephosphorane they said was caused by the increased reactivity of this species which opposed the formation of the equilibrium between betaine and reactants allowing the stereochemical outcome to be determined by the relative ease of betaine formation.

House, Jones and Frank²⁰ recently reported the results of a series of reactions involving both stable and unstable ylides in different solvents in the presence of added inorganic salts and with two aldehydes of differing reactivity. They found that stereochemically the reaction of carbomethoxymethylenetriphenylphosphorane and acetaldehyde is practically unaffected by changes in the polarity of the solvent in going from methylene chloride to 1,2-dimethoxyethane to chloroform to dimethylformamide. They did find that solutions of lithium salts regardless of the anion give increased yields of the cis isomer. However, they also found that a

protonic solvent such as methanol is even more effective than added salts in increasing the proportion of cis olefin. They furthermore found that chloroacetaldehyde gives increased amounts of the cis isomer compared to acetaldehyde.

To explain these results they propose coordination of the carbonyl oxygen by a Lewis acid (either ROH or Li^+) which could then effect the stereochemical outcome in the following way (Figure 2).

The interconversion of the intermediate solvated betaines by either a reversal of the formation reaction or through some intermediate ylide resulting from a loss of a proton from either C or D may be slower than the interconversion of A and B. If the rates of decomposition of the betaine remain unaltered then the reaction would be less stereoselective. House pointed out that even if the rate of interconversion of the betaines is not retarded by solvation the concentration of the solvated betaines should be different than the concentration of unsolvated betaines because the stabilities of the solvated betaines would be more nearly equal than the unsolvated betaine in which the trans would be more stable. He based these conclusions on a consideration of the interactions of the non-bonded groups in the preferred conformations.

House also reported in this paper a repetition of work done by Shemyakin and Bergelson in which he finds that the latter's results for the reaction of benzyldiene-triphenylphosphorane and propionaldehyde in the presence of added LiBr and LiI are much too high. On repeating these experiments Shemyakin and Bergelson found their results to be closer to those of House but that significant differences, particularly in the case of the dimethylformamide solvent system still exist.

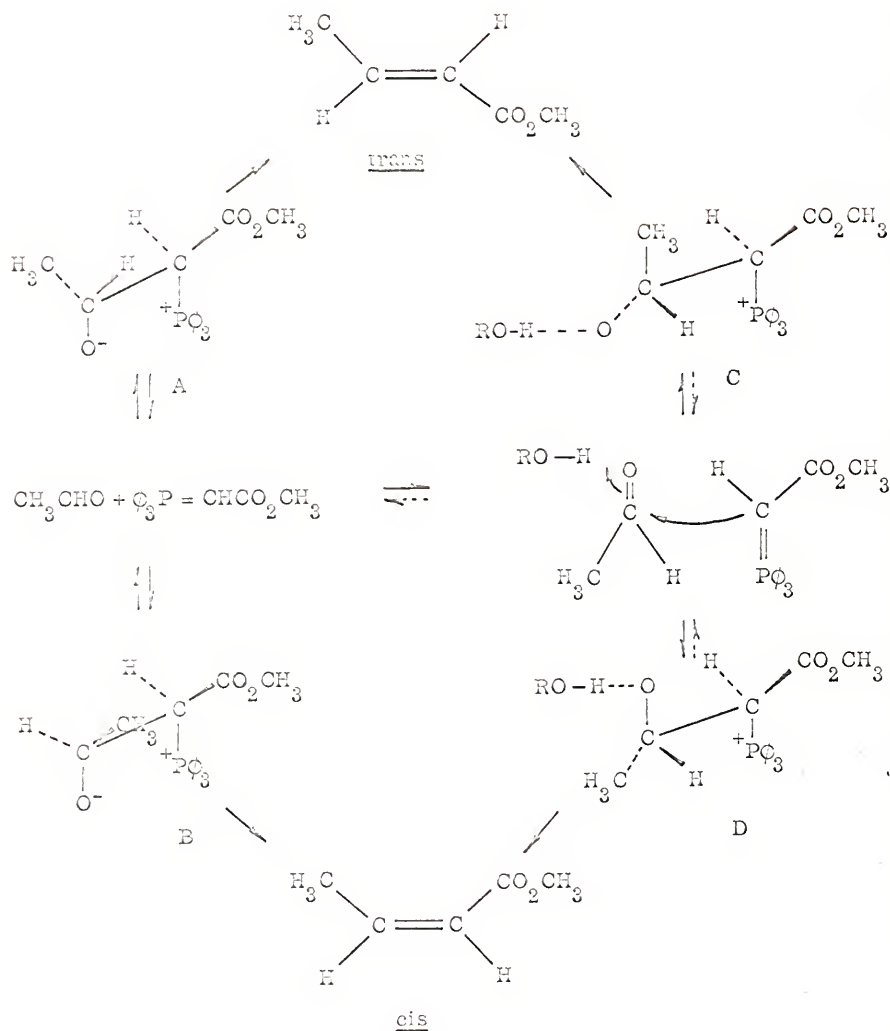
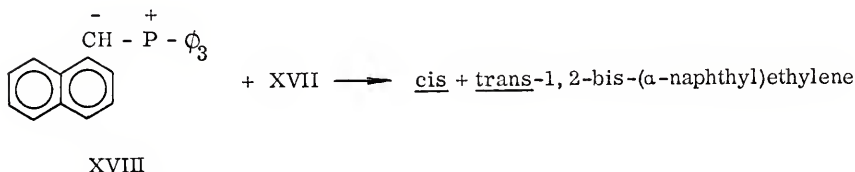
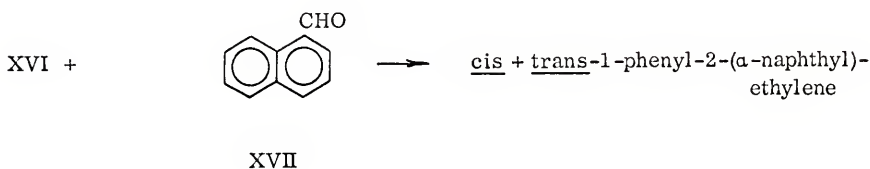
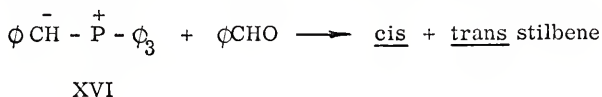


Figure 2. Postulated Reaction Paths of the Wittig Reaction

In 1964 Drefahl, Lorenz and Schnitt²¹ conducted a study of the effects of various solvents, bases, reaction temperatures, anions, reaction times and reactant concentrations on the stereochemistry of the Wittig reaction. These effects were studied on one or all of the following reactions:



These workers found that changes in the reaction temperature, anion, reaction time and reactant concentrations have no effect on the stereochemistry of the resulting olefin. However, they observed that the bases sodium carbide and sodium amide in benzene and tetra hydrofuran respectively produced a marked decrease in the amount of cis isomer whereas butyl lithium in benzene produced a slight increase in the cis isomer, all compared to sodium ethoxide in the respective solvents. Their study of solvents showed that ethanol, methanol and aniline give approximately the same cis:trans ratio (58:42), compared to these solvents chloroform gives an increased amount of cis isomer and ethyl ether, tetra hydrofuran, dioxane, benzene,

pyridine, methylene chloride, carbon tetrachloride, acetonitrile, nitrobenzene and dimethylformamide give a decreased amount of cis isomer. They offer no explanation of these results.

In summary it appears that few conclusions or generalizations can be drawn concerning either the mechanism or the stereochemistry of the Wittig reaction at the present time. The studies thus far conducted have produced controversy rather than clarity--testimony to the complexity of the reaction. Furthermore, large gaps still exist in our knowledge of certain aspects of the synthesis. This is particularly true of the reactions of unstable or reactive ylides which is the subject of the research to be described.

Statement of the Problem

As a result of research^{22, 23} in Dr. G. B. Butler's group on the synthetic aspects of the Wittig synthesis a number of interesting observations were made which had previously received little or no attention in the literature. In surveying the literature it became apparent that the stereochemistry of the reaction had also been largely untouched. It seemed appropriate then to study these several aspects of the Wittig reaction at the same time since they are logically related.

The objective of this research was to study the effect of certain factors on the stereochemistry of the Wittig reaction. The system chosen was one leading to the isomeric 1,3-pentadienes. The factors to be studied were:

- 1) solvents
- 2) temperature
- 3) reaction time
- 4) relative concentration of reactants

- 5) nature of the anion
- 6) nature of substituents.

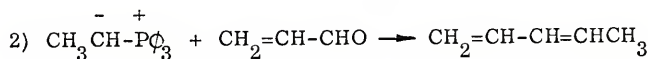
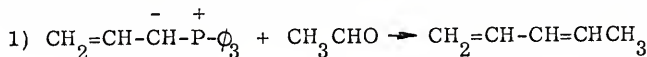
In addition, the possibility of a 1,4-addition of ylide to a conjugated carbonyl system was to be studied.

Method of Attack

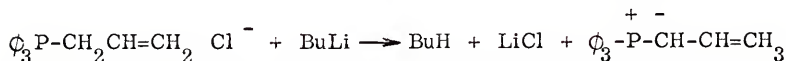
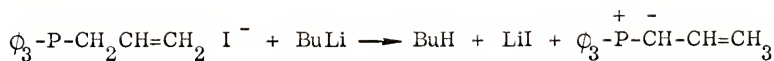
The choice of the 1,3-pentadiene system was based on the following considerations. First, the olefin is well characterized. Second, it is highly volatile which was an essential property in our experimental procedure. Third, since it is the first member of the homologous 1,3-dienes exhibiting geometrical isomerism it should be of general interest. Fourth, no work had previously been reported on this system.

As it turned out the choice was fortunate since the reactivity of the allylidene-triphenylphosphorane lies between the more widely studied stable ylides and the unstable or reactive ylides. This should permit the ready correlation of existing data across the spectrum of ylide reactivities encountered in the Wittig reaction.

The approach was to synthesize 1,3-pentadiene by the Wittig reaction in three different ways as shown. Each of the three ylides shown could be prepared from



three different phosphonium salts. These nine salts were obtained or prepared



and used in investigating the nature of the anion effect.

The reaction starting with allyltriphenylphosphonium bromide, acetaldehyde and butyl lithium in equimolar amounts was chosen as a standard and used to investigate the other factors enumerated. The standard solvent was tetrahydrofuran, the standard reaction temperature was 0° C. and the standard reaction time was 120 seconds. These conditions were chosen for convenience and through experience gained in preliminary work with the system.

Because of the number of reactions to be run a semi-micro technique was employed using 1.0 millimole quantities of reactants and analyzing the products by previously standardized vapor phase chromatography. The reactions were conducted in an all glass manifold under nitrogen and no mechanical transference of the products was required until the time of analysis.

A few auxiliary experiments were carried out so that appropriate comparisons could be made with a somewhat different system.

CHAPTER II

DISCUSSION AND RESULTS

Solvents

Reactions in which the effect of the solvent was determined were carried out in the standard procedure except a test solvent rather than THF was added to the ylide.

The results of these experiments are listed in Table 3. It is obvious that the effect of solvent on the stereochemistry with but two exceptions is negligible. On the other hand, the effect of solvent on the yield is considerable. In going from decalin to *N,N*-diethylaniline one observes a 400 per cent increase in the yield. One notes that though there is a crude correlation existing between yield and the dielectric constant of the solvent several exceptions occur.

Both *n*-butyl and *t*-butyl alcohols give only traces of 1,3-pentadiene under these reaction conditions. This is not altogether unexpected since the allylidenetriphenylphosphorane is a very strong base, much stronger than the conjugate bases of these two alcohols. It appears that the addition of these alcohols initiates an acid-base reaction in which most of the ylide is converted to phosphonium salt.

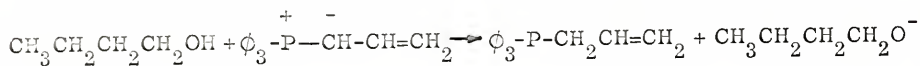


TABLE 3.

SOLVENT EFFECTS

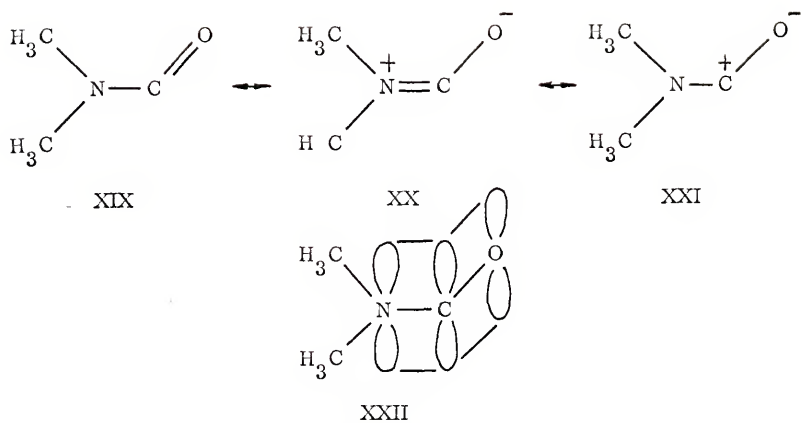
| <u>Solvent</u> | <u>% Yield</u> | <u>Cis : Trans</u> | <u>Dielectric Constant</u> |
|-------------------------|----------------|--------------------|----------------------------|
| Decalin | 13 | 42:58 | 2.2 |
| Toluene | 21 | 41:59 | 2.38 |
| Triethylamine | 29 | 43:57 | 3.1 |
| N,N-Dimethylaniline | 50 | 42:58 | 4.4 |
| N,N-Diethylaniline | 18 | 41:59 | 5.20 |
| Tetrahydrofuran | 45 | 42:58 | 7.6 |
| <u>t</u> -Butyl Alcohol | 0.7 | 50:50 | 11.4 |
| <u>t</u> -Butyl Alcohol | 0.9* | 50:50 | 11.4 |
| <u>n</u> -Butyl Alcohol | 20.3 | --- | 17.8 |
| N,N-Dimethylformamide | 17 | 53:47 | 37.6 |

*20 Min. reaction time

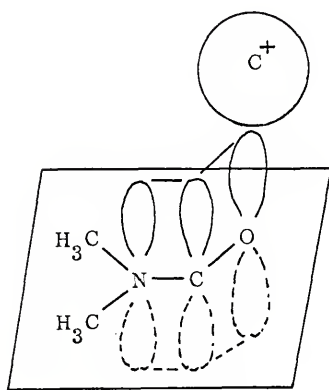
Three observations were made concerning the reaction in the butyl alcohols. First, the fact that some 1,3-pentadiene is obtained at all seems to indicate that an equilibrium does exist but that it is displaced far to the right. Second, further evidence for the equilibrium is obtained in the reaction of t-butyl alcohol in which the reaction time is lengthened from two minutes to twenty minutes. Though this is a small change it is in the expected direction. Third, the fact that the yield of product is greater in t-butyl alcohol than in n-butyl alcohol is in keeping with the proposed equilibrium since the t-butoxide ion is a stronger base than the n-butoxide ion and should cause the equilibrium to be shifted to the left.

Concerning the stereochemistry of the above two reactions it would seem unwise to place much significance on the cis-trans ratios observed since the yields are so low and the relative error so high.

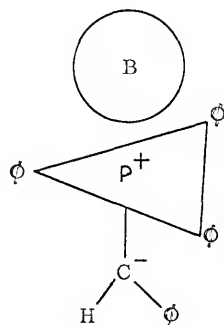
The case of N,N-dimethylformamide (DMF) is peculiar in two respects. It produces a 25 per cent increase in the amount of cis 1,3-pentadiene in the product mixture whereas the yield is reduced to practically one-third of that observed in tetrahydrofuran (THF) the next most polar solvent. This anomalous behavior is rather difficult to explain. Shemyakin and Bergelson¹⁰ felt that the enhancement of the yield of the cis isomer which they observed for reactions carried out in DMF vs THF is caused by an interaction between the phosphorus of the ylide and the strongly polarized oxygen of the DMF. This proposal seems unlikely for two reasons. First, DMF, because of resonance stabilization represented by forms XX and XXII exists as a planar molecule.²⁴ As a planar molecule with high π electron density (forms XX and XXI) on the oxygen its mode of solvation of an electrophilic center would be through a line perpendicular to the plane of the molecule. The solvation of



the ylide phosphorus would appear difficult from steric considerations if the DMF molecule assumes the same configuration as that described by Bergelson and Shemyakin for other Lewis bases.



XXIII



XXIV

Second, it has been shown that DMF is a particularly effective solvent²⁵ for cations such as alkali metal cations. It therefore seems likely that the species solvated would be the lithium cation rather than the phosphorus of the ylide.

If this is the case and if the ylide exists as an ion-pair as Schlosser²⁶ has suggested, the amount of "free" ylide would increase in DMF in contrast to less specific cation solvents. This would result in a more rapid but less selective attack of ylide on aldehyde. This seems to be a more plausible explanation than that of the Russian workers.

The low yields with DMF have been observed previously by House²⁰ and Shemyakin.¹⁹ Both of these workers found yields in DMF to be lower than those in benzene. However, neither of them has offered an explanation of this behavior. The possibility of side reactions seems improbable since we observed no peaks in our chromatograms different from those seen using THF. Also other workers have obtained under somewhat different conditions and using different starting materials, yields in excess of 90 per cent. The only speculation that can be offered at present is that the DMF may form a relatively stable complex with the intermediate betaines thereby decreasing the rate of betaine decomposition to products.

The case of the amines is also difficult to explain. There appears to be a steric effect operating in the solvation process which favors the somewhat less hindered DMA over DEA but no other conclusions can be drawn at this time. One added observation was made during the course of the solvent study. When the ylide is first generated in decalin it is an orange-red suspension. The addition of toluene and DEA has a negligible effect on deepening the color or increasing the

solubility of the ylide. However all of the other solvents except the alcohols caused increased or complete solution of the ylide and an intensification of the color to a very deep red. The alcohols each reacted a bit differently. The n-butanol formed a yellow-orange solution that contained a small amount of white solid while the t-butyl alcohol produced a brownish-red solution containing a larger amount of solid. The increased solubility in the more polar solvents is to be expected but more study is necessary before conclusions can be drawn regarding the bathochromic shifts observed.

Temperature Effects

These reactions were carried out in the standard procedure except that the ice bath surrounding the reaction tube was replaced by the following baths. For the room temperature bath water which had come to equilibrium at room temperature was used. For the bath at -20°C a mixture of magnesium nitrate hexahydrate and crushed ice was used. For the -78°C bath Dry Ice and acetone was used.

From the data in Table 4 one may see that over the temperature range covered no significant change in the cis-trans ratio takes place. However, the yield is increased by 30 per cent as one proceeds from room temperature to -78°C . This is probably the result of diminishing the rate of side reactions relative to the rate of olefin formation. The nature of the side reaction or reactions was not extensively explored in the present work but Butler and Hauser²² have postulated a competing aldol condensation as being responsible for the low yields generally obtained with aliphatic aldehydes.

A side reaction that was noted in these experiments was the production of

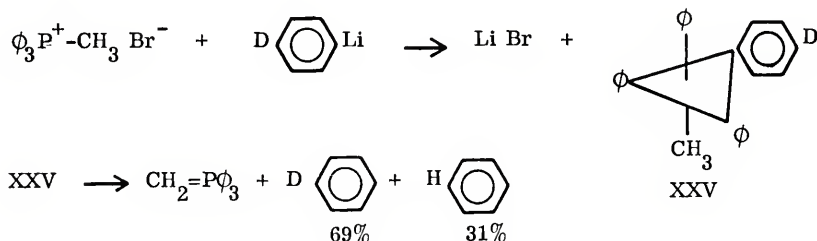
TABLE 4.

TEMPERATURE EFFECTS

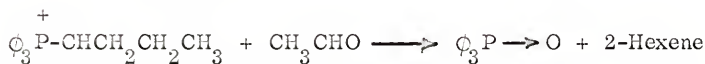
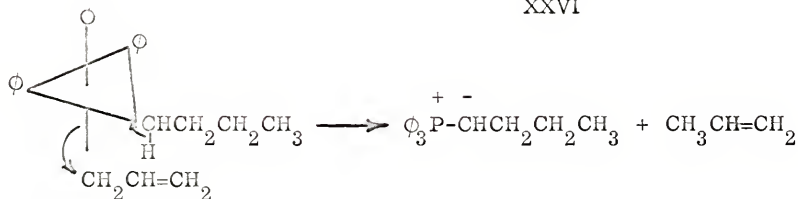
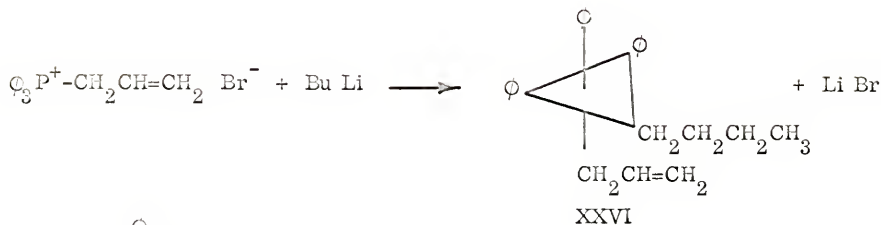
| <u>Temperature</u> | <u>% Yield</u> | <u>Cis : Trans</u> |
|--------------------|----------------|--------------------|
| 27°C. | 41 | 42 : 58 |
| 0°C. | 45 | 42 : 58 |
| -20°C. | 49 | 43 : 57 |
| -78°C. | 53 | 43 : 57 |

cis and trans 2-hexene. As one goes from higher to lower temperatures one notes that the relative amount of the 2-hexenes produced decreases from 3.6 to 0. The number 3.6 represents approximately 2 mole per cent of isomeric 2-hexenes. Therefore this is not the only side reaction taking place.

The production of the 2-hexene may be rationalized in at least two ways. Seyferth²⁷ and co-workers have found evidence for pentavalent phosphorus intermediates in the formation of ylides and proposed the mechanism shown below. The fact that both deuterobenzene and the hydrogen substituted benzene are produced

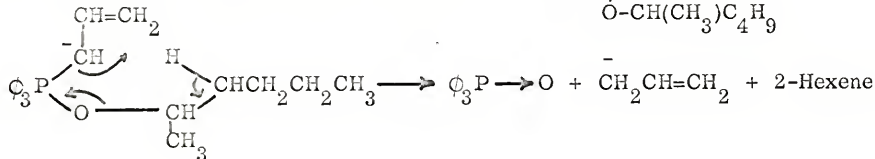
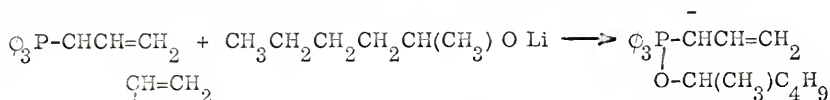


is indicative of either a structure such as XXV or an exchange mechanism. Seyferth favors the formation of a pentacovalent intermediate. Whether an analogous mechanism is responsible for the 2-hexenes is open to question since Seyferth noted that the reaction of methyl lithium with a benzyltriphenylphosphonium salt gave no benzene. He concluded that in certain cases only hydrogen abstraction took place. The only supporting evidence we have for such a reaction sequence besides the product is the detection of small amounts of propene in our product mixture. However this propene could arise from the reaction of unreacted ylide with the water quench. That such reactions take place has been demonstrated by Fenton and



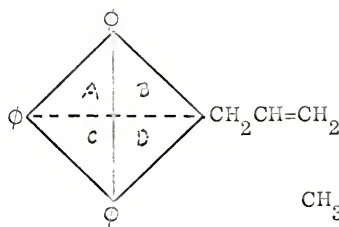
and Ingold.²⁸ These workers in examining a series of phosphonium hydroxides found the order in which groups are displaced is $\text{C}_6\text{H}_5 > \text{P} > \text{alkyls}$. Since we also found benzene in our product mixtures it is difficult to decide for or against this path.

The other route to the 2-hexenes involves the addition of butyl lithium to acetaldehyde and the subsequent elimination reaction as outlined.

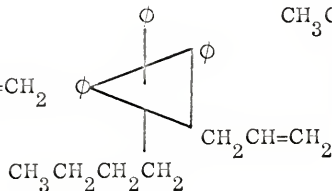


Speziale and Ratts²⁹ have postulated a similar path for the reaction of dichloromethylenetriphenylphosphorane in t-butyl alcohol which yielded considerable amounts of isobutylene. An objection to this path would be that no 1-hexene was observed along with 2-hexene. However considering the small amount of the more stable 2-hexene formed this would be understandable.

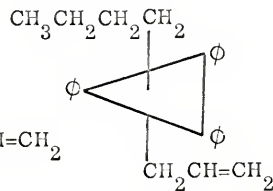
One might conclude that if the second reaction path is in effect, the production of the 2-hexenes would always be accompanied by the formation of propene and vice versa. If this is true we can rule out this path since several cases were noted where propene was liberated but no 2-hexene could be detected. Returning to the first reaction path one might reason similarly except that here there is an optional reaction path. Instead of the allyl group abstracting the proton from the butyl group, a phenyl could be used in which case benzene would be a by-product rather than propene. Benzene is observed to be a product but the nature of the ylide is difficult to rationalize unless we take certain geometrical characteristics of the species into consideration. The allyltriphenylphosphonium cation probably has tetrahedral symmetry. If we proceed through a pentacovalent structure this species must arise from the attack of the butyl lithium on one of the sides labeled A, B, C or D.



XXVIII



XXIX



XXX

If the attack takes place on sides A, B or D we obtain the trigonal bipyramid XXIX. If the attack occurs on side C we obtain structure XXX. If we take into account the relative basicities of the three species we find that they decrease in this order $n\text{-butyl} > \emptyset \geq \text{allyl}$. The acidities would conceivably be in the reverse order however the phenyl carbon attached to phosphorus has no hydrogen to donate leaving just allyl and butyl groups to compete in this decomposition to ylide. Considering structure XXIX it seems probable that the more acidic allyl group would donate its proton to the butyl group giving butane. In structure XXX the strongly basic butyl group is no longer in position to accept a proton from the allyl group and so there would be a competition between the two acidic groups allyl and butyl to donate a proton to a phenyl. Since the acidity of the allyl group is greater than that of the butyl more allylidenebutyldiphenylphosphorane would be formed than butyldieneallyldiphenylphosphorane. This is also true of structure XXIX but the probability would undoubtedly be reduced because of the favorable positions of the acidic allyl and basic butyl groups. Also one notes that structure XXIX is statistically favored by 3:1 over XXX. Whether all the ylide is produced through intermediates XXIX and XXX is an open question as is the existence of such intermediates.

Perhaps the best evidence for this reaction path is based on the stereochemistry of the 2-hexenes formed. In fourteen experiments under varying conditions ten gave an excess of the cis-2-hexene, two gave an excess of trans-2-hexene and two were about 1:1 ratios. The predominance of cis isomer seems to be diagnostic of a reactive ylide which the butyldienephosphorane is. If the other mechanism were correct one might expect either a statistical distribution or a preponderance of the more stable trans isomer.

Reaction Times

In Table 5 are the results for reactions carried out under standard conditions but with variable reaction times. One observes that no change in the stereochemistry of the products takes place over the range of times covered. The yield shows about a 10 per cent increase in going from the 30 second to the two minute reaction time but apparently levels out beyond this.

Of greatest significance in this series of reactions is the extremely fast rate at which the reaction proceeds. It was hoped that rough kinetics could be obtained for the reaction during this series but this proved to be impossible under the experimental conditions used. In the absence of kinetic data a great deal can not be said concerning the mechanism or the transition states of this reaction except by analogy.

A kinetic study is of utmost importance in obtaining an understanding of the mechanisms and stereochemistry of the reaction. It would appear to be the next logical step in this research area.

TABLE 5.

REACTION TIMES

| <u>REACTION TIME</u> | <u>% YIELD</u> | <u>CIS:TRANS</u> |
|----------------------|----------------|------------------|
| 30 sec. | 40 | 42:58 |
| 120 sec. | 45 | 42:58 |
| 1200 sec. | 46 | 42:58 |

Concentration Effects

During this series of experiments all the standard conditions were in effect except that varying amounts of phosphonium salt, acetaldehyde and butyl lithium were used. The results of these experiments is given in Table 6.

From the Table it is evident that varying the reactant concentrations produces no significant change in the stereochemistry of the resulting olefin. The very slight increase in the cis olefin produced by the doubling of both aldehyde and phosphonium salt concentrations may or may not be significant since it lies just beyond the range of the average deviation.

Of more interest is the fluctuation in yield that one observes. Doubling the concentration of butyl lithium produces a sharp drop in olefin yield for three possible reasons. First, the excess butyl lithium may add across the carbon-oxygen double bond. Second, being a strong base it may initiate aldol type condensation reactions. Third, it may polymerize the 1,3-pentadiene produced. These reactions represent well known modes of reaction of organolithium compounds, and could occur singly or together. During the runs in which the butyl lithium concentration was doubled large quantities of viscous polymeric materials were observed to form in the reaction tube which would be indicative of the last two reactions. However, no attempt was made to isolate or identify such by-products.

Reactions in which the acetaldehyde concentration was doubled or the butyl lithium and phosphonium salt concentrations were doubled though they appear comparable proved to be otherwise from a yield standpoint. Whereas the excess aldehyde resulted in an increased yield of olefin compared to the reaction using equimolar amounts of reactant, the excess amount of ylide caused a slight decrease

TABLE 6
CONCENTRATION EFFECTS

| Concentration (mmoles/6 ml. solvent) | | | | |
|--|---------|-------------------------|---------|-----------|
| $\phi_3\text{-P}^+\text{-CH}_2\text{CH=CH}_2\text{Br}$ | n-Bu Li | CH_3CHO | % Yield | Cis:Trans |
| 1 | 1 | 1 | 45 | 42:58 |
| 2 | 1 | 1 | 50 | 43:57 |
| 1 | 2 | 1 | 16 | 43:57 |
| 1 | 1 | 2 | 59 | 43:57 |
| 2 | 2 | 1 | 41 | 43:57 |
| 2 | 1 | 2 | 75 | 45:55 |

in the yield of olefin. The latter result may be rationalized by noting the strongly basic properties of the ylide and its ability to induce base catalyzed condensations of the aldehyde. The increase in yield produced by doubling the aldehyde concentration was expected. If the rate expression for this class of ylides is similar to the expression obtained by Speziale and Bissing⁸ for stable ylides then the rate would be proportional to the ylide concentration multiplied by the aldehyde concentration. We might expect twice the amount of product for this reaction provided there were no side reactions and that the reaction was still in its early stages where this kinetic expression would be linear. However, as was observed in our experiments on the reaction time, this reaction is very fast. It begins to level off in approximately 30 seconds. Under these circumstances we would not expect to observe a doubling of yield with a doubling of the aldehyde concentration but an increase of variable magnitude.

Doubling the concentration of phosphonium salt would appear to have little effect on the yield since it should not alter the concentration of either reactant. However, the data shows that this conclusion is not completely correct.

An examination of the chromatograms from the reaction of equimolar amounts of ylide and aldehyde under varying conditions invariably reveals the presence of small amounts of n-butane. The exact amount of n-butane cannot be ascertained because of the overlap of the n-butane peak with the propene peak which is almost always present and the lack of calibration for n-butane with the internal standard. However, to make a very rough estimate the n-butane would probably be around 5 mole per cent plus or minus 3 per cent. This represents the n-butyl lithium left after the reaction has been completed. The n-butane is formed by the hydrolysis

of this unreacted n-butyl lithium with the aqueous quench. Although the chromatogram from the reaction using double salt concentration does not reveal a decrease in the amount of n-butane it shows an increase in the amount of propene produced. This is comparable to an increase in the amount of ylide which would account for the increased yield. The point of this rationale is that the reaction between the phosphonium salt and n-butyl lithium does not go to completion under the reaction conditions used in this work. This leaves a fair amount of n-butyl lithium (perhaps more than 10 mole per cent) free in solution to react with the aldehyde thus decreasing the yield. The additional phosphonium salt converts part of this unreacted n-butyl lithium to ylide in which state it can then react with aldehyde to give an increased amount of product. The observation that no 2-hexene is formed in this particular reaction is probably caused by increasing the odds for normal hydrogen abstraction from the allyl group rather than the butyl group by increasing the number of phosphonium ions present.

The highest yield was observed to occur when both the phosphonium salt and acetaldehyde concentrations alone led to increased yields of 1,3-pentadiene. The magnitude of the increase suggests a synergistic effect which may be explained by reasoning similar to that used for the increase accompanying the doubling of the salt concentration. Since the increased amount of salt would form more ylide and we now have a large excess of aldehyde with which it may react, one would expect a substantial increase in yield.

Substituent Effects

In this series of reactions standard conditions were used except that the nature

TABLE 7.

SUBSTITUENT AND ANION EFFECTS

| No. | $R-P^+\phi_3 X^-$ | | $R'-CHO$ | Yield | Cis: Trans |
|-----|-------------------|--------|-------------|-------|------------|
| | R | X^- | R' | | |
| 1 | $CH_2=CHCH_2-$ | I^- | CH_3- | 42 | 48:52 |
| 2 | $CH_2=CHCH_2-$ | Br^- | CH_3- | 45 | 42:58 |
| 3 | $CH_2=CHCH_2-$ | Cl^- | CH_3- | 21 | 42:58 |
| 4 | CH_3CH_2- | I^- | $CH_2=CH-$ | 17 | 61:39 |
| 5 | CH_3CH_2- | Br^- | $CH_2=CH-$ | 40 | 59:41 |
| 6 | CH_3CH_2- | Cl^- | $CH_2=CH-$ | 47 | 74:26 |
| 7 | $CH_2CH_2CH_2-$ | Br^- | CH_3- | -- | 71:29* |
| 8 | CH_3CH_2- | Br^- | CH_3CH_2- | -- | 72:28* |

* Product is 2-pentene

of the phosphonium salts and aldehydes was varied. From Table 7. one observes a very striking change in the stereochemical outcome of the reaction as one changes either the aldehyde or the salt. When one exchanges the "R" group attached to the aldehyde and ylide in reaction 1 through 6 the cis to trans isomer ratio is reversed.

In reactions 7 and 8 we can see the effect of replacing a vinyl group in the allyl ylide or acrolein with an ethyl group. The result is a 75 per cent increase in the cis isomer for allyl ylide and a 20 per cent increase for acrolein. To be sure these systems are not strictly comparable since the product of allyl ylide and acetaldehyde and ethyl ylide and acrolein give 1,3-pentadiene while ethyl ylide and propionaldehyde and propyl ylide and acetaldehyde give 2-pentene as the product. However the two systems are similar enough so that the conclusions regarding the stereochemistry involved should be fairly valid.

Since all of the ylides used in this work are "reactive" ylides we may assume that the initial step in the reaction, betaine formation is very fast. It follows then that this process will be unselective giving equal amounts of "cis" and "trans" betaines. Since the ratio of products in no case shows this exact 1:1 cis to trans ratio it would seem probable that the equilibrium postulated for unreactive and less reactive ylides must also be operating here.

Assuming the attainment of an equilibrium between ylide and aldehyde and the isomeric betaines one must conclude that the factor determining the stereochemistry is the relative magnitude of the rate constants for dissociation and decomposition of betaine as expressed by Speziale and others. The key word here is magnitude since similar arguments have been made in rationalizing products containing greater than 95 per cent trans isomer down to 50:50 ratios. If one makes several assump-

tions one can arrive at a fairly satisfactory rationalization of the entire range of Wittig reactions.

First it is assumed that in the initial attack of ylide upon aldehyde, unreactive ylides are more selective giving a predominance of "trans" betaine compared to reactive ylides. In comparing conformation of the ensuing betaines (Figure 3) one observes that the largest effect on the orientation of ylide and aldehyde is played by the electrostatic attraction between the developing opposite charges. For unreactive ylides, conformations leading to XXXIII and XXXVII would be the least likely of those shown. Of the remaining possibilities conformation leading to "trans" betaines would be favored over those leading to "cis" betaines. The case for reactive ylides would be quite different since betaine formation is very rapid and hence less selective perhaps to the point of being statistical.

Second, in the absence of any stabilization, other than weakly inductive effects, the decomposition of "cis" betaine will be favored over the "trans." Further, the placement of the stabilizing group on the carbon attached to the phosphorus will have a greater effect than if attached to the carbonyl carbon. These stabilizing groups described will either exhibit a (+R) and a (-I) effect e.g. - Cl or - ϕ or a (-R) and (-I) effect e.g. - $C\equiv N$ or - COOR. However, if one is dealing with an unreactive ylide the addition of an electron withdrawing group to the aldehyde will generally increase the amount of "cis" betaine since it will increase the reaction rate and lower the selectivity of betaine formation.

The postulate that a "cis" betaine will decompose to olefin (cis) faster than the "trans" betaine when not stabilized is not without precedent. There are cases of steric acceleration in the literature although none are strictly analogous to the

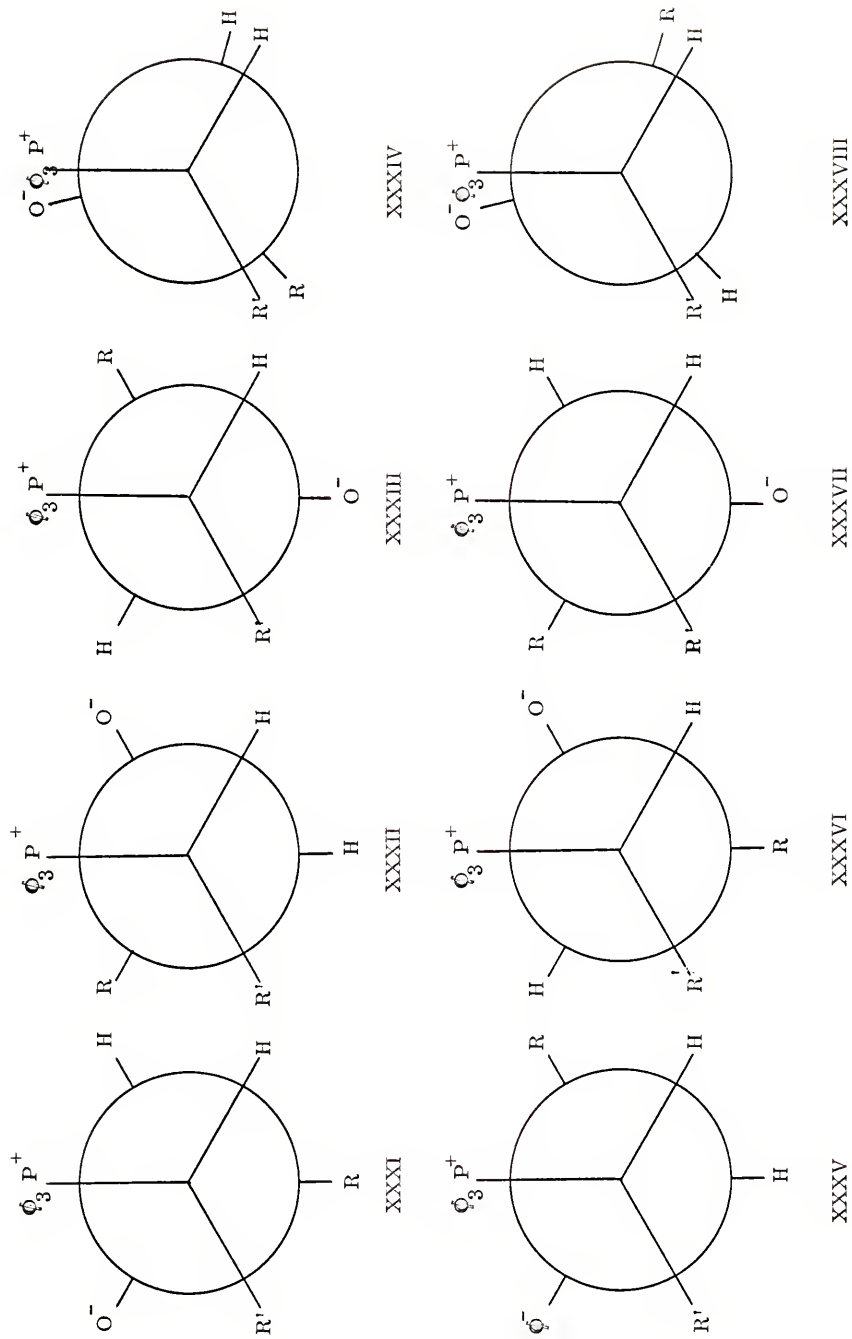
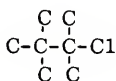
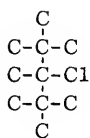


Fig. 3 Possible Betaine Configurations

present system. Brown and Berncis³⁰ showed that the solvolysis of halide XXXIX is twenty-one times as fast as t-butyl chloride XLI and that XL is five hundred times as fast. Since one could not possibly ascribe such differences to inductive or hyperconjugative effects Brown reasoned that the phenomenon could best be



XXXIX



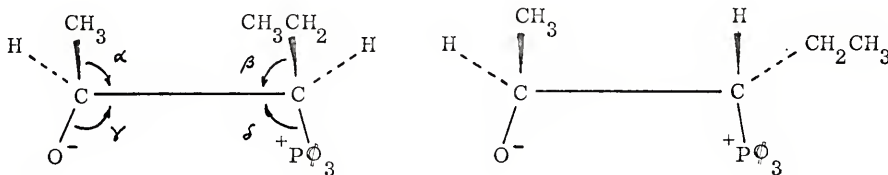
XL



XLI

explained by the release of steric strain. The chlorides on ionization give carbonium ions in which the dihedral angle between the alkyl substituents is increased from 109° to 120° .

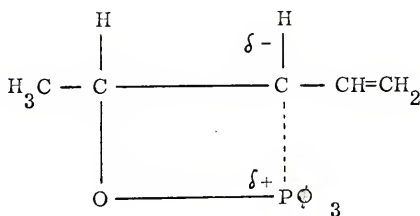
If we consider the two possible betaine configurations involved in the formation of 2-pentene we can see that as the methyl group eclipses the ethyl group in

cis XLIItrans XLIII

the "cis" configuration the repulsive interaction produced will increase the bond angles $\underline{\alpha}$ and $\underline{\beta}$. At the same time angles $\underline{\gamma}$ and $\underline{\delta}$ will decrease slightly and the distance between negatively charged oxygen and positively charged phosphorus will decrease. In the case of the "trans" betaine this extra push toward phosphorus-

oxygen bond formation is not structurally possible. Since there exists an equilibrium between the two betaines via reactants, the observed isomer ratio can thus be rationalized.

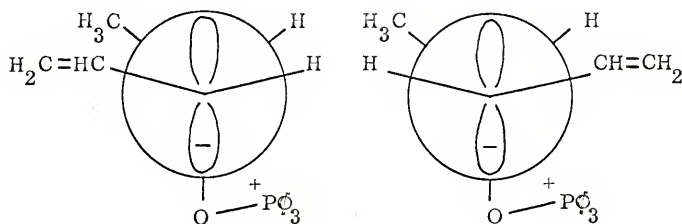
Turning to the reaction of allyl ylide and acetaldehyde in which the products consisted of a 42:58 ratio of cis to trans 1,3-pentadiene we would predict that the allyl ylide though very reactive is less reactive than an alkyl ylide. Therefore, the initial attack on aldehyde would be somewhat slower and a bit more selective, giving more "trans" than "cis" betaine. In this case since we have a stabilizing group present, located on the carbon attached to phosphorus, it should have a substantial effect in altering the stereochemical outcome of the reaction. XLIV represents a possible transition state leading from betaine to olefin. This structure shows the cyclized betaine in the process of breaking a phosphorus-carbon bond.



XLIV

That this bond should break rather than the carbon-oxygen would be predicted on the difference in bond energies which is about 7 kcal/mole, the release of steric strain and the probability that this is an axial bond making it somewhat weaker than a normal tri- or tetra-covalent carbon-phosphorus bond. As charge is developed on carbon (2) the ability of the vinyl group to delocalize it will be

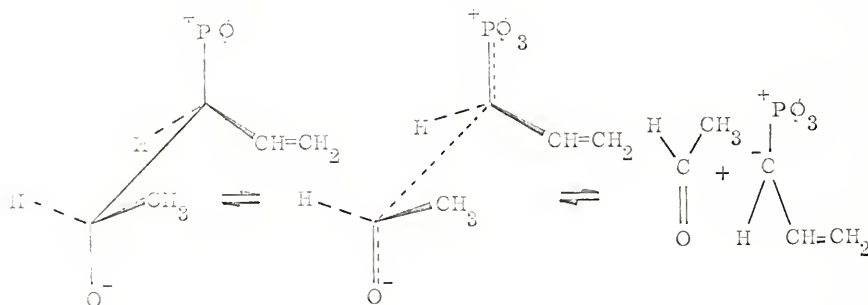
dependent on its ability to lie in a plane passing through carbons (1) and (2) and perpendicular to the departing phosphorus. XLV and XLVI show that stabilization of the developing negative charge and the double bond can be best accomplished for steric reasons when the vinyl and methyl groups are trans to one another.

cis XLVtrans XLVI

The 50 per cent increase in cis isomer obtained on exchange of the vinyl and methyl groups between aldehyde and ylide as shown in reactions 4, 5 and 6 can be explained in a similar manner. We now have a more reactive ylide than the allyl ylide which should give us less selectivity in betaine formation with an increased amount of "cis" betaine. A transition state similar to that pictured for the allyl ylide-acetaldehyde case would show that since the vinyl is not attached to a center of primary charge-formation the stabilization of the intermediate through a coplanar vinyl group is of less importance than the steric acceleration promoting decomposition of the "cis" betaine.

Using the foregoing assumptions one can justify other examples of predominant cis olefin as reported in the literature in a similar manner.

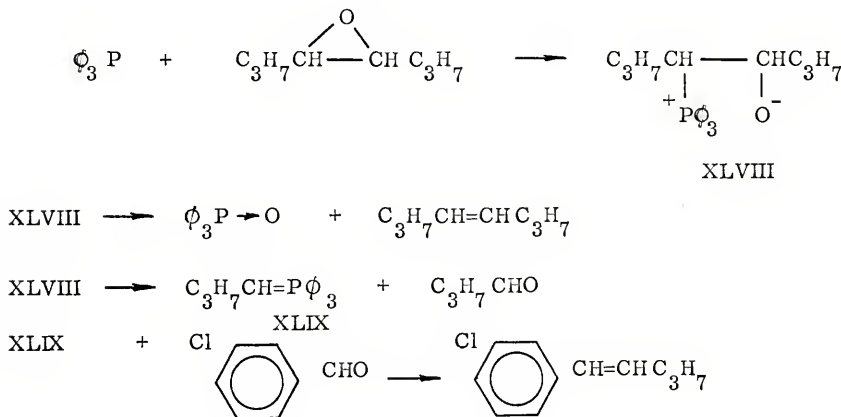
There is one point which we have neglected in the foregoing argument--the dissociation of betaine. XLVII represents a possible transition state for betaine dissociation. We assume the conformation shown since this structure should lead



to the least electrostatic attraction between the oxygen and phosphorus and thus be the least likely state for betaine decomposition to olefin. In this proposed transition state we have the partial breaking of the C₁ - C₂ bond with a shifting of the bonding pair of electrons to C₂, the ylide carbon. This situation necessarily means that C₁ will be somewhat electron-deficient and C₂ somewhat electron-rich. Stabilization of such a transition state and an accompanying increased rate of dissociation would result if electron withdrawing groups were attached to C₂ and electron-donating groups were attached to C₁.

Using this reasoning we would conclude that in the series studied in this work, the rate of dissociation would decrease in the following order:
 allyl ylide + acetaldehyde > ethyl ylide + acrolein > ethyl ylide + propionaldehyde = propyl ylide + acetaldehyde. The relationship of these rates to the stereochemical outcome of the reaction arises from the ensuing equilibrium between reactants

and betaine. However conclusions cannot be drawn without taking into account the rate of betaine decomposition. Furthermore, the relative rates of dissociation of the isomeric betains must be considered. Bissing and Speziale³¹ have recently published work in which they have determined the relative rates of dissociation vs decomposition for three systems. Starting with isomeric 4-octene oxides they treat these with triphenylphosphine generating the betaine in situ. If an excess of the more reactive m-chlorobenzaldehyde is present any butyridene-triphenylphosphorane formed through equilibration would react with it in preference to butyraldehyde giving 1-(m-chlorophenyl)-1-pentene. The ratio of 1-(m-chlorophenyl)-1-pentene to 4-octene would then be an indication of the ratio of betaine dissociation to betaine decomposition. They find for the 4-octene oxides this



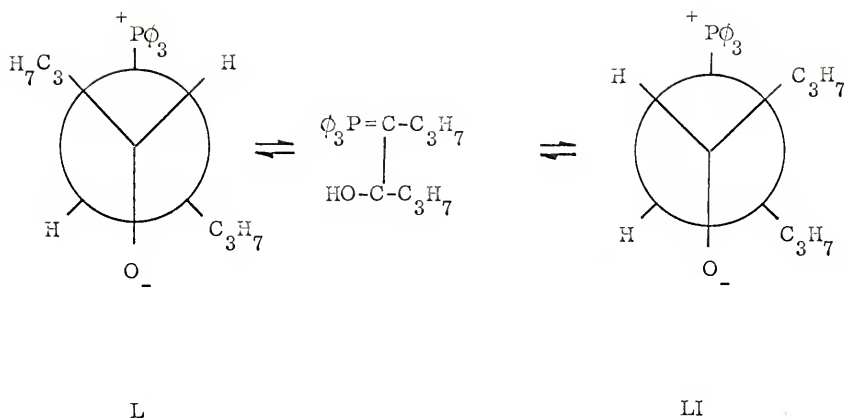
ratio to be quite small indicating that the rate of betaine dissociation for unstabilized betaines is low. They also found that this ratio increases for stilbene oxide and ethyl phenylglycidates which we would also expect. Their work on the 4-octene oxides and stilbene oxides is particularly interesting since it also reveals infor-

mation concerning the relative rate of dissociation of "cis" and "trans" betaines. Table 8 shows the results of their work with the pure isomeric epoxides. They assumed that a cis epoxide would lead to trans betaine and trans epoxide would lead to cis betaine.

TABLE 8.

| RING OPENING REACTIONS OF 4-OCTENE OXIDE AND STILBENE OXIDE | | | | |
|---|------------|--------------|---|--------------|
| Epoxide | % 4-Octene | | % 1-(<u>m</u> -chlorophenyl) -1- pentene | |
| | <u>cis</u> | <u>trans</u> | <u>cis</u> | <u>trans</u> |
| <u>cis</u> 4-octene oxide | 31 | 55 | 6 | 9 |
| <u>trans</u> 4-octene oxide | 73 | 12 | 7 | 9 |
| <u>cis</u> stilbene oxide | 21 | 23 | 12 | 44 |
| <u>trans</u> stilbene oxide | 22 | 22 | 16 | 39 |

If all of their assumptions are correct only three products should result from each isomeric epoxide. In the case of cis-4-octene oxide one should obtain trans-4-octene and cis and trans 1-(m-chlorophenyl)-1-pentene. However we see that a fairly large amount of cis-4-octene is also produced and the second isomer arises in the other two reactions as well. The authors state that the "forbidden" isomer may arise from either direct attack of the triphenylphosphine on oxygen of the epoxide or from a proton exchange.



The point to be observed here is that the ratio of betaine dissociation to betaine decomposition is the same for "cis" and "trans" betaine derived from 4-octene-oxide and from stilbene oxide. Though this conclusion may be correct for the stilbenes it is not correct for the octenes. The fact that the "cis"-4-octene betaine gives 73 per cent cis 4-octene while the "trans"-4-octene betaine gives only 53 per cent trans -4-octene is indicative that the rates of betaine decomposition are quite different. The authors state that the reliability of the dissociation to decomposition ratio is probably not too high so it seems probable that the rate of betaine decomposition is higher for the "cis" than the "trans" betaine whereas for dissociation the reverse is true.

We can rationalize the latter phenomenon by considering models of a possible transition state leading to dissociation for the isomeric betaines. Since no stabilizing groups are attached to the carbon atoms making up the bond about

to be broken the difference in the energy of the transition state should be a reflection of steric considerations alone. In the "trans" structure there will result a skew interaction between the adjacent *n*-propyl groups which is absent in the "cis" structure. If we invoke steric acceleration we would predict the "trans" isomer to dissociate to reactants faster than the "cis." However, when one or both of the *n*-propyl groups are replaced by stabilizing groups such as vinyl, carbomethoxy, etc., the reverse would be true since the ability of that group to stabilize the charged center would be dependent on its ability to become co-planar. It could accomplish this much more easily in the "cis" structure than in the "trans".

Anion Effects

In looking at the data in Table 7 we note two reactions which gave higher proportions of the cis-1,3-pentadiene than the others. The reaction using allyltriphenylphosphonium iodide gives a 48:58 ratio. The reaction of ethyl-triphenylphosphonium chloride gives a 74:26 cis:trans ratio while the other ethyl-phosphonium salts give a 60:40 ratio. Whether we are observing a halide effect or an experimental error cannot be said with certainty. The latter is a possibility only because the explanation of the former postulation is so difficult.

Shemyakin and Bergelson¹⁹ reported a result similar to ours for reactions 4 and 6. They reacted propyridenetriphenylphosphorane with benzaldehyde in ethyl ether to give β -ethyl styrene in the presence of added lithium halides.

Their results are shown in Table 9. Their results exhibit the same trends in yield and stereochemistry as ours.

TABLE 9.

ANION EFFECTS

| $\text{CH}_3\text{CH}_2\text{CH}=\text{P}\phi_3 + \phi\text{CHO} \quad \text{CH}_3\text{CH}_2\text{CH}=\text{CH}\phi + \phi_3\text{P} \quad \text{O}$ | | | | |
|---|------|------------|-------|------------------|
| Solvent | Salt | Ylide:RCHO | Yield | <u>Cis:Trans</u> |
| EtOEt | LiCl | 1:1 | 70% | 80:20 |
| EtOEt | LiI | 1:1 | 46% | 22:78 |
| ϕH | LiCl | 1:1 | 62% | 79:21 |
| ϕH | LiI | 1:1 | 33% | 35:65 |

In another series of experiments³² these investigators reacted the ylide derived from benzyltriphenylphosphonium chloride and iodide with propionaldehyde in benzene. With the chloride they obtained a 20:80 cis to trans ratio while with the iodide they obtained a 41:59 ratio. They gave no yield data. This reflects a similar increase in the amount of cis isomer we experienced in comparing reactions (3) and (1). The benzyl and allyl ylide are roughly comparable and we have demonstrated the absence of a solvent effect for this system so that the analogy is not without some merit.

Even if we can justify our results by comparing it with the work of others there still remains the need of a better explanation or a satisfactory mechanism.

Regarding the question of a "halide effect" we have two opposite schools of thought. Shemyakin and Bergelson feel the effect is caused by the halide ion acting on the phosphorus of the ylide while House believes that it is caused by a lithium cation acting on the oxygen of the carbonyl function.

Whatever the mechanism of this effect it seems clear from our results and those of the Russians that it is of a synergistic nature. The presence of a specific halide (cation) only has an effect on the stereochemistry when a specific ylide is used. When used with a different ylide no effect on the stereochemistry is produced.

There appears to be no explanation for these results at the present time. Too few data are available on the solubilities and other factors which certainly have a bearing on this phenomenon. Until we have such data it seems best to avoid unsubstantiated postulates.

1,4-Addition and Isomerization

The reactions in Table 10 were carried out under standard conditions except the specified methylphosphonium salts and crotonaldehyde were used. The commercially available crotonaldehyde is apparently almost all trans isomer. V.p.c. analysis showed but one peak on two different columns but there is still the possibility that neither column could resolve the mixture of isomers.

From the Table 10 one observes a constant cis-trans isomer ratio of 5 : 95. This indicates that if the starting aldehyde was a 5 : 95 mixture of cis and trans

isomers no isomerization took place under the reaction conditions used, that is ,

TABLE 10.

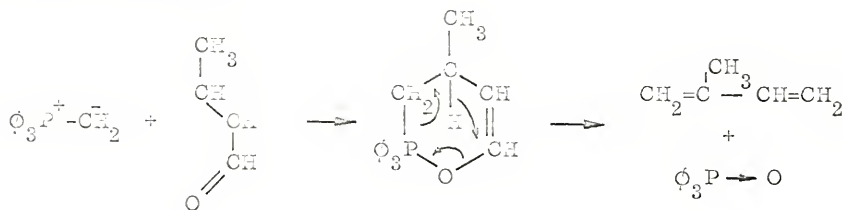
REACTIONS OF METHYLTRIPHENYLPHOSPHORANES
WITH CROTONALDEHYDE

| Salt | % Yield | <u>cis-trans</u> |
|-----------------------------------|---------|------------------|
| Me P ⁺ I ⁻ | 19 | 5:95 |
| MeP ⁺ Br ⁻ | 17 | 5:95 |
| Me P ⁺ Cl ⁻ | 25 | 5:95 |

standard conditions.

The increased yield with the chloride may be indicative of a "halide effect" as discussed in the previous section.

The other purpose for running this series of experiments was to see if a possible 1,4-addition of the ylide to aldehyde would take place. There are several references^{33,34,35} in the literature to such reactions but none have been reported for such a simple system as crotonaldehyde. If 1,4-addition occurred it would do so by the path shown.



LIII

No evidence for such a reaction occurring was concluded by the observation that no isoprene is formed.

To further show that no isomerization took place under our reaction conditions a small amount of pure trans 1,3-pentadiene was added to the reaction between methylenetriphenylphosphorane and acetaldehyde. No cis 1,3-pentadiene was observed among the products.

CHAPTER III

EXPERIMENTAL

Equipment and Data

All temperatures are reported in degrees centigrade and are uncorrected. Pressures are reported in millimeters of mercury as determined by either a Zimmerli or McLeod gauge.

Infrared spectra were either obtained with a Perkin-Elmer Infracord or a Beckman IR 10 under the conditions noted.

Refraction indexes were obtained using a Bausch and Lomb Abbe 34 Refractometer equipped with an achromatic compensating prism.

Vapor phase chromatography (v.p. c.) was carried out on a F and M Model 700 chromatograph using a hydrogen flame-ionization detector and the columns and conditions stipulated.

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

Source and Purification of Materials

The absence of water and purity of the solvents and aldehydes were checked by infrared and v.p.c. analysis on two columns having the following specifications:

8 ft. 10% Carbowax 20M on 60-80 mesh Diatoport S

8 ft. 10% Silicone Fluid (Nitrile) on 60-80 mesh Diatoport S

The temperatures and flow rates for the v.p.c. analysis were selected to give optimum resolution.

Distillations at atmospheric pressure were carried out under nitrogen.

Solvents

Tetrahydrofuran was J. T. Baker reagent grade material. It was pre-dried over "Dri-Na" for several days, then refluxed with and distilled from lithium aluminum hydride. B.p. 66.3-66.4°C., $n_D^{20.1}$ 1.4078; lit. (36) b.p. 65.4°C., n_D^{20} 1.407. The infrared spectrum showed a trace of water which may have been introduced into the exceedingly hygroscopic solvent during sampling. V.p.c. on both columns showed a single peak.

Decalin was Fisher Laboratory Grade--a mixture of cis and trans isomers. It was washed successively with three portions of concentrated sulfuric acid, three portions of 5 per cent aqueous sodium hydroxide and four portions of distilled water. It was dried overnight with anhydrous calcium chloride or "Dri-Na" and distilled under vacuum, a 10 per cent forerun being discarded. Infrared examination showed water to be absent and v.p.c. showed just two peaks.

Triethylamine was "white label" grade obtained from Distillation Products Industries, Division of Eastman Kodak Company. It was refluxed with and distilled from anhydrous barium oxide. B.p. 88.7-88.8°C., $n_D^{21.2}$ 1.4005; lit. (37) b.p. 89.3°C., n_D^{20} 1.4003. Infrared showed a trace of water and v.p.c. showed just one peak.

Toluene was J. T. Baker reagent grade material. It was distilled, discarding the first one-third of the distillate. B.p. 110.0°C., $n_D^{20.8}$ 1.4968; lit. (38) b.p.

110.6°C., n_D^{20} 1.4969. Infrared showed no water to be present and v.p.c. showed but one peak.

N,N-diethylaniline was "white label" grade "mono-free" material obtained from Distillation Products Industries Division of Eastman Kodak Company. It was refluxed with and distilled from anhydrous barium oxide under reduced pressure. B.p. 52.6-52.7°C./0.8 mm $n_D^{20.8}$ 1.5417; lit. (39) b.p. 217.5°C./760 mm $n_D^{22.3}$ 1.5411. Infrared showed no water or primary and secondary amine to be present. V.p.c. showed a single peak.

N,N-dimethylaniline was "white label" grade "mono-free" material obtained from Distillation Products Industries of Eastman Kodak Company. It was refluxed with and distilled from anhydrous barium oxide under reduced pressure. B.p. 63.5°C./2.0 mm $n_D^{21.0}$ 1.5581; lit. (40) b.p. 194.2°C./760 mm, n_D^{20} 1.5587. Infrared showed the absence of water or primary and secondary amines. V.p.c. showed a single peak on the Carbowax column and a small shoulder of less than 1 per cent total area on the Silicon column.

N,N-dimethylformamide was reagent grade material obtained from Fisher Scientific Company. It was refluxed with and distilled from anhydrous barium oxide, b.p. 149.5°C., $n_D^{20.4}$ 1.4301; lit. (41) b.p. 153°C., $n_D^{22.4}$ 1.4294. Infrared showed a trace of water present. V.p.c. showed a single peak.

n-Butyl alcohol was reagent grade material obtained from J. T. Baker Chemical Company. It was refluxed with and distilled from sodium and di-n-butyl phthalate. B.p. 118.5-118.7°C., $n_D^{20.4}$ 1.3995; lit. (42) b.p. 118°C., n_D^{20} 1.3991. V.p.c. showed a single peak.

tert-Butyl alcohol was J. T. Baker reagent grade material. It was refluxed with and distilled from sodium metal. B.p. 83.7-83.8° C., $n_D^{20.3}$ 1.3867; lit. (42) b.p. 82.6° C., n_D^{20} 1.3878. V.p.c. showed a single peak.

Aldehydes

Acetaldehyde was "white label" grade material obtained from Distillation Products Industries Division of Eastman Kodak Company. It was distilled through a 12-inch vacuum-jacketed Vigreux column. The condenser temperature was kept at approximately 10° C. by external cooling. B.p. 22-23° C.; lit. (43) b.p. 20.2° C. V.p.c. showed a single peak.

Acrolein was "white label" grade material obtained from Distillation Products Industries Division of Eastman Kodak Company. It was dried with anhydrous magnesium and sodium sulfates then distilled. B.p. 52.5-52.7° C.; lit. (44) b.p. 52.5° C. Infrared showed a trace of water. V.p.c. on the Carbowax column showed two small extra peaks of total area approximately 1 per cent. Only one small peak besides that of acrolein was noted on the silicone column.

Crotonaldehyde was "white label" grade material obtained from Distillation Products Industries, Division of Eastman Kodak Company. It was dried with anhydrous magnesium sulfate and distilled. B.p. 102.9-103.2° C., $n_D^{20.4}$ 1.4370; lit. (45) b.p. 102.2° C., $n_D^{20.5}$ 1.4362. Infrared showed a trace of water to be present. V.p.c. showed a single peak.

Miscellaneous Chemicals

Samples of cis and trans-1,3-pentadiene, cis and trans-2-hexene and cis and trans-2-pentene were obtained from Chemical Samples Company. V.p.c. analysis of these compounds was carried out on a 25 ft. β , β' -oxydipropionitrile

column.

Cis-1,3-pentadiene shows characteristic infrared absorption⁵⁴ at 771 cm^{-1} .
V.p.c. gives a single peak. n_D^{21} 1.4367; lit. (52) n_D^{20} 1.4363.

Trans-1,3-pentadiene exhibits characteristic infrared absorption⁵⁴ at 814 cm^{-1} . V.p.c. shows a small peak in addition to the main peak. This small peak precedes the larger and constitutes approximately 5-10 per cent of the larger peak.
 n_D^{21} 1.4298; lit. (52) n_D^{20} 1.4301.

Cis-2-hexene exhibits characteristic infrared absorption⁵³ at 691 cm^{-1} .
V.p.c. shows a very small peak preceding the main peak. n_D^{21} 1.3974; lit. (52) n_D^{20} 1.3977.

Trans-2-hexene exhibits characteristic infrared absorption⁵³ at 964 cm^{-1} .
V.p.c. shows a small peak preceding the main peak. The area of the small peak is approximately 3-5 per cent of the main peak. n_D^{21} 1.3941; lit. (52) n_D^{20} 1.3935.

Cis-2-pentene exhibits characteristic infrared absorption⁵³ at 696 cm^{-1} .
V.p.c. shows a very small peak preceding the main peak. $n_D^{21.7}$ 1.3832; lit. (52) n_D^{20} 1.3830.

Trans-2-pentene exhibits characteristic infrared absorption⁵³ at 964 cm^{-1} .
V.p.c. shows a single peak. $n_D^{21.7}$ 1.3791; lit. (52) n_D^{20} 1.3793.

Ethyl acetate, 2-propanol, benzene and carbon tetrachloride which were used as solvents in the recrystallization of the phosphonium salts were Fisher reagent grade chemicals.

The methyl isobutyl ketone and chloroform used in recrystallizations were reagent grade chemicals obtained from J. T. Baker Chemical Company. The 95 per cent ethanol used in recrystallizations was obtained from Union Carbide Chemical

Corporation.

All of the above were used without further purification.

Ethyl iodide was obtained from Columbia Organic Chemical Company and was used without further purification.

Triphenylphosphine and methyl iodide were obtained from Peninsular ChemResearch, Incorporated and was used without further purification.

Allyl chloride, ethyl bromide and n-propyl bromide were obtained from Distillation Products Industries Division of Eastman Kodak Company. The allyl chloride and ethyl bromide were redistilled before use; the n-propyl bromide was used as received.

The Nalcite SAR 20-50 mesh anion (chloride) exchange resin was obtained from National Aluminate Corporation.

The butyl lithium in hexane was supplied by Foote Mineral Company. The butyl lithium was assayed using the procedure of Kamienski and Esmay.⁵⁵

Preparation and Purification of Phosponium Salts

Methyltriphenylphosphonium bromide, allyltriphenylphosphonium chloride and allyltriphenylphosphonium bromide were on hand having been used in previous research by Dr. Butler's group.

Methyltriphenylphosphonium iodide was prepared from methyl iodide and triphenylphosphine in benzene according to the procedure of Wittig and Schollkopf⁵ in 54 per cent yield.

Ethyltriphenylphosphonium bromide was prepared from ethyl bromide and triphenylphosphine in benzene by the procedure of Wittig et al. in 50 per cent yield.

Ethyltriphenylphosphonium iodide was prepared from ethyl iodide and tri-

phenylphosphine in benzene by the procedure of Wittig et al. in 75 per cent yield.

Methyltriphenylphosphonium chloride was prepared in two ways. First, 18.7 g. (0.1 mole) of silver nitrate were dissolved in 50 ml. of distilled water followed by treatment with an excess of 6 M HCl. The precipitated silver chloride was filtered and washed with distilled water, then added to a suspension of 40.4 g. (0.1 mole) of methyltriphenylphosphonium iodide in 200 ml. of water. The suspension was refluxed with stirring for four hours. The suspension was allowed to cool, then filtered with suction. The aqueous filtrate containing the methyltriphenylphosphonium chloride was evaporated to dryness on a rotary evaporator. The solid remaining was dissolved in a small amount of chloroform, transferred to an evaporating dish and the solvent evaporated. The amorphous white salt was produced in 101 per cent yield (if anhydrous).

Second, to a 4 ft. by 1 in. O.D. Pyrex column charged with 0.5 lbs. of Nalcite SAR anion exchange resin in the chloride form was added 5.14 g. of methyltriphenylphosphonium bromide in one litre of distilled water. The effluent was evaporated to dryness on a rotary evaporator giving a small amount of white, amorphous methyltriphenylphosphonium chloride.

Ethyltriphenylphosphonium chloride was prepared using the first procedure described above for methyltriphenylphosphonium chloride.

Allyltriphenylphosphonium iodide was prepared by the procedure of Wittig et al. using triphenylphosphine and allyl iodide in benzene. The yield was 96 per cent. The allyl iodide was prepared by the procedure of Letsinger and Traynham⁴⁶ from allyl chloride and sodium iodide in acetone.

n-Propyltriphenylphosphonium bromide was prepared by the procedure of Wittig et al. using triphenylphosphine and n-propyl bromide in benzene.

All data concerning the physical constants, analyses, crystallization solvents etc., for the above salts are summarized in Table 11.

Apparatus

The reactions were run in the all glass apparatus shown in Figure 4. The stopcock (A) connects the manifold to a tank of Linde "high purity" nitrogen. The nitrogen is passed through a drying tower containing indicating Drierite. Stopcock (B) connects the manifold to the reaction tube (G). Stopcock (C) connects the manifold to the receiver (H). Stopcock (D) connects the manifold to the vacuum pump through either a Dry Ice and acetone or liquid nitrogen cooling trap. Outlet (E) leads to a Zimmerli gauge and stopcock (F) connects the system to the atmosphere through a silicone oil bubbler and mercury trap in series.

The reaction tubes, receivers, syringes, etc., were all dried for several hours at 130° C. before use.

Reactants

The phosphonium salts which had already been dried once were weighed to the nearest milligram into a tared weighing bottle on an analytical balance. The salts were then dried in a vacuum oven overnight at 100° C., removed to a desiccator and stored there until used. The weight loss incurred on this second drying was usually less than 0.5 milligrams but in the case of the chlorides almost a stoichiometric amount of water was removed from the monohydrate. Appropriate corrections were made in the procedure for these salts.

TABLE 11
PHYSICAL CONSTANTS OF PHOSPHONIUM SALTS

| R-P ⁺ -O ₃ ⁻ X ⁻ R | Recrystallization | | *m.p. 0° C. | Lit. m.p. (Ref.) | Analyses (found) | | | Analyses (calcd.) | | | |
|--|-------------------|------------|-------------|------------------|------------------|-------|------|-------------------|-------|------|------|
| | X ⁻ | Solvent(s) | | | 1 st. | 2 nd. | C | H | P | C | H |
| CH ₂ =CH-CH ₂ CH ₂ =CH-CH ₂ | I ⁻ | F | G | 227-230 | -- | 58.36 | 4.58 | 7.27 | 58.63 | 4.69 | 7.20 |
| | Br ⁻ | C | A | 219-220 | 209-214 (47) | 65.79 | 5.34 | 8.07 | 65.80 | 5.26 | 8.08 |
| | | | | | | 65.74 | 5.30 | | | | |
| CH ₂ =CH-CH ₂ CH ₂ =CH-CH ₂ | Cl ⁻ | B | D | 227-228 | 225-227 (21) | 72.50 | 6.62 | 4.03 | 74.46 | 5.95 | 9.15 |
| | | | | | | 74.60 | 6.10 | | | | |
| CH ₃ CH ₂ CH ₃ CH ₂ | I ⁻ | A | A | 168-169 | 164-165 (48) | 55.88 | 4.62 | 7.14 | 57.43 | 4.82 | 7.41 |
| | | | | | | 57.50 | 4.93 | 7.40 | | | |
| CH ₃ CH ₂ CH ₃ CH ₂ | Br ⁻ | C | A | 207-208 | 203-205 (49) | 62.65 | 5.44 | 8.40 | 64.70 | 5.43 | 8.34 |
| | | | | | | 64.86 | 5.60 | | | | |
| CH ₃ CH ₂ | Cl ⁻ | E | D | 240-241 | 234-236 (50) | 73.17 | 6.17 | 9.46 | 73.50 | 6.17 | 9.48 |
| CH ₃ CH ₃ | I ⁻ | A | A | 186-187 | 188-189 (1) | 56.62 | 4.25 | 7.84 | 56.46 | 4.49 | 7.67 |
| | Br ⁻ | A | A | 231-232 | 229-232 (1) | 63.95 | 5.17 | 8.75 | 63.89 | 5.08 | 8.67 |
| CH ₃ CH ₃ | Cl ⁻ | E | D | 221-222 | 212-213 (48) | 72.59 | 5.98 | 9.93 | 72.69 | 5.80 | 9.91 |
| | | | | | | | | | | | |
| CH ₃ CH ₂ CH ₂ | Br ⁻ | A | - | 236-237 | 229-230 (51) | 65.65 | 5.60 | 7.99 | 65.12 | 6.24 | 8.00 |
| | | | | | | 65.38 | 5.97 | | | | |

* All salts were dried at 100° C. for from 12-24 hours in a vacuum oven. A = isopropyl alcohol; B = tert. butyl alcohol; C = 1:1 isopropyl alcohol:methyl isobutyl ketone; D = 1:3 isopropyl alcohol:ethyl acetate; E = 3:3:1:1 ethyl acetate:methyl isobutyl ketone:chloroform:n-butanol; F = 2:3 isopropyl alcohol:abs. ethyl alcohol; G = 95% ethyl alcohol.

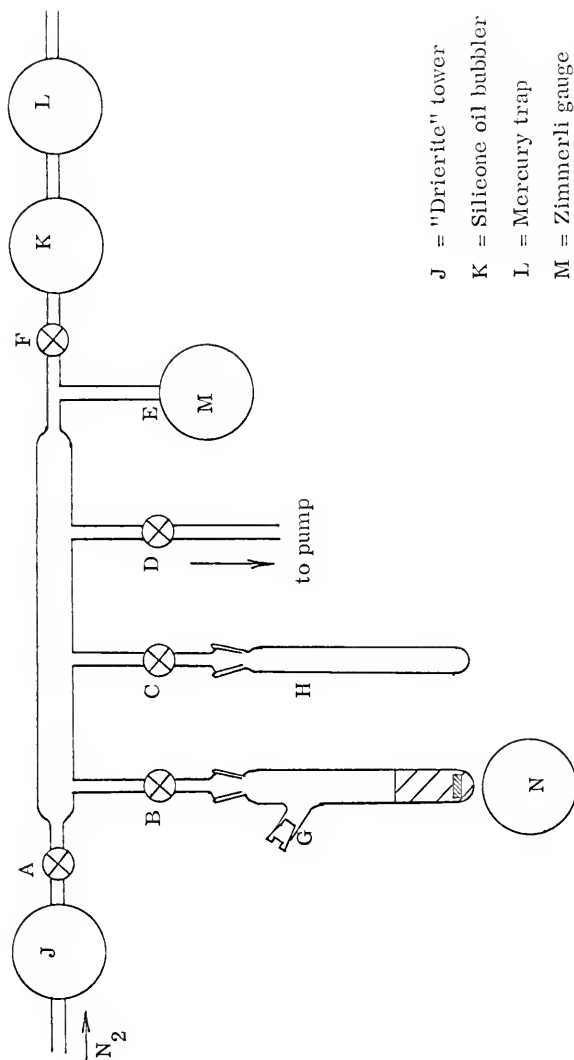


Figure 4. Reaction Manifold

The aldehyde solutions in decalin were made up by weight on an analytical balance. For acetaldehyde because of its volatility, five milliliter samples were made up - enough for two runs. For acrolein and crotonaldehyde both five and ten milliliter samples were used. Acetaldehyde solutions were used the same day and kept in the refrigerator between runs as were the other aldehydes. In the case of acrolein, its solutions were protected from light until the sample was withdrawn from introduction into the reaction tube. Since the solutions of aldehydes were made up in volumetric flasks this work was carried out in the dark room at approximately 20° C. The aldehyde solutions were withdrawn from the volumetric flasks using a five milliliter syringe which had previously been flushed with nitrogen several times. The syringe was overfilled, inverted and the plunger brought to the 2.0 ml. mark. Since the same syringe was always used along with the foregoing procedure only small errors in the amount of aldehyde introduced should have occurred.

The butyl lithium solution was kept in a 100 cc. amber bottle under nitrogen sealed with a syringe cap. The bottle was kept inclined with the cap up so that salts resulting from decomposition or hydrolysis of the reagent would collect at the bottom of the bottle. Care was taken to obtain clear solutions of the reagent in the one milliliter syringe perviously flushed with nitrogen. Again the same syringe was always used for the butyl lithium solutions.

The tetrahydrofuran was kept in a 50 milliliter 2-necked flask under nitrogen. When a sample was to be withdrawn a stream of nitrogen was first led into the flask at a moderate rate before the second stopper was removed and the THF withdrawn with a syringe.

Other solvents were used immediately after distillation and such rigid precautions were not found necessary.

The Reaction

The following description is what may be called a standard procedure because it was this procedure or a variation of it that was used throughout this work. This standard procedure involves the reaction between allylidenetriphenylphosphorane (derived from allyltriphenylphosphonium bromide) with acetaldehyde in equimolar amounts using tetrahydrofuran as the solvent. The reaction time is 120 seconds, the reaction temperature is 0°C. The other reactions in this work are but variations of one of these parameters--a different temperature, etc. However, in any experiment only one parameter is varied. The remainder are kept constant.

One millimole of phosphonium salt is transferred by a funnel from the weighing bottle to the reaction tube containing a small stirring bar. The side arm is closed with a serum cap and 2.0 ml. of decalin is introduced by pipet. The reaction tube is then attached to the manifold and with stopcocks (A) and (F) closed and (B), (C) and (D) open the system is evacuated. During this evacuation the stirrer is activated to aid in degassing the suspension. After approximately five minutes stopcock (D) is closed and stopcock (A) opened carefully to readmit nitrogen to the system. This process is repeated two more times. After the nitrogen has been admitted the third time stopcock (F) is opened and the flow rate of nitrogen decreased.

0.595 ml. (1 millimole) of butyl lithium is now added to the reaction tube with a syringe through the serum cap. The suspension rapidly changes color from yellow to orange to brick red. After two minutes stopcocks (A) and (F) are closed and the system is evacuated. During this 30-minute evacuation period n-butane and the hexane that was used as a solvent for the butyl lithium is removed. The boiling point of decalin is sufficiently high so that little of it is removed in this evacuation process. The allylidenetriphenylphosphorane and unreacted butyl lithium are non-volatile. At the end of this evacuation, stopcock (A) is opened and nitrogen readmitted to the system. Stopcock (F) is then opened to restore the system to atmospheric pressure.

2.0 ml. of tetrahydrofuran are then introduced into the reaction tube by means of a syringe and the blood red solution is allowed to stir for ten minutes. At the end of the ten minute period a slush ice bath is placed around the reaction tube and the reaction mixture is allowed to equilibrate for two minutes. Stopcock (B) is then closed and 2.0 ml. of acetaldehyde (1 millimole) in decalin is introduced by syringe into the reaction tube over a one minute period. The addition of the aldehyde solution generally results in the formation of a white solid and a lightening of the red color. After two minutes 1.0 ml. of distilled water is added by syringe. This produces complete decolorization almost immediately with the formation of a two phase liquid-liquid system. After two minutes the reaction tube is frozen out with liquid nitrogen for three minutes. The system is evacuated after opening stopcock (B) and closing stopcocks (A) and (F). The evacuation to less than 1 mm takes approximately four minutes after which stopcock (D) is closed and the liquid nitrogen bath is transferred from the reaction tube (G) to the receiver (H).

As the reaction tube warms the volatile materials distill or sublime into the receiver. The distillation is continued for 40 minutes. About half-way through the distillation period the stirrer is activated to promote the transfer of the volatile materials. At the completion of the distillation nitrogen is readmitted through stopcock (A), stopcock (F) is opened and the liquid nitrogen bath removed from the receiver. When the contents of the receiver have melted the receiver is disconnected from the manifold, sealed with a serum cap and removed to the dark room (20° C.) where 30 μ l. of cyclohexene the internal standard is added. The mixture is then either analyzed immediately by v.p.c. or the receiver is kept in a Dry Ice and acetone bath until the analysis is performed.

Analysis

The analyses were all run on the F and M Model 700 using a 25 ft. x 1/4 in. O.D. column containing 10 per cent by weight of β, β' -oxydipropionitrile on 60-80 mesh Chromosorb P. The column temperature was $250 \pm 1^\circ \text{C}$. and the flow rate approximately 75 ml. per minute. The size of the sample injected was 0.3 μ l.

Calibration of the Internal Standard

A series of synthetic mixtures containing known amounts of trans-1,3-pentadiene and cyclohexene, the internal standard, were prepared in tetrahydrofuran in concentrations such that the sensitivity setting of the chromatograph would be the same or very close to those used during the actual runs. The samples were made up by volume at 20° C. For example, the "known" containing 50 mole per cent 1,3-pentadiene was prepared in the following way. Into a small vial flushed with N_2 and sealed with a serum cap was placed 0.7 ml. of tetrahydrofuran.

Next 10.04 $\mu\text{l.}$ of cyclohexene was added followed by 5.0 $\mu\text{l.}$ of trans-1,3-pentadiene. The mixture was shaken well and then at least two 0.3 $\mu\text{l.}$ portions were chromatographed under the same conditions as those used for the actual runs.

In between runs the vials were kept in a Dry Ice-acetone bath. The calculations used to arrive at the volume of internal standard and pentadiene are as follows:

$$\text{Gram Molecular weight cyclohexene} = 82.1 \text{ g.}$$

$$\text{Density at } 20^{\circ}\text{C. cyclohexene} = 0.811 \text{ g./ml.}$$

$$\text{Gram Molecular weight 1,3-pentadiene} = 68.1 \text{ g.}$$

$$\text{Density at } 20^{\circ}\text{C. of 1,3-pentadiene} = 0.676 \text{ g./ml.}$$

$$\begin{aligned} 1.000 \mu\text{l. } \underline{\text{trans}}\text{-1,3-pentadiene} &= ? \text{ gram-moles} \\ &= 1 \mu\text{l.} \times 10^{-3} \text{ ml. } \mu\text{l.}^{-1} \times 0.676 \text{ g.} \\ &\quad \text{ml.}^{-1} \times 1 \text{ mole } 68.1 \text{ g.}^{-1} \end{aligned}$$

$$1.000 \mu\text{l.} = 9.93 \times 10^{-6} \text{ moles } \underline{\text{trans}}\text{-1,3-pentadiene}$$

$$9.93 \times 10^{-6} \text{ moles cyclohexene} = ? \mu\text{l.}$$

$$\begin{aligned} \mu\text{l.} &= 9.93 \times 10^{-6} \text{ moles} \times 82.1 \text{ g. mole}^{-1} \times 1 \text{ ml. } (0.811 \text{ g.})^{-1} \times \\ &\quad 1 \mu\text{l. } 10^{-3} \text{ ml.}^{-1} \end{aligned}$$

$$9.93 \times 10^{-6} \text{ moles} = 1.004 \mu\text{l. cyclohexene}$$

Therefore if we want a 50 mole per cent solution of 1,3-pentadiene we would use 0.500 $\mu\text{l.}$ 1,3-pentadiene for each 1.004 $\mu\text{l.}$ cyclohexene. Since we used 5.00 $\mu\text{l.}$ of 1,3-pentadiene we would use 10.04 $\mu\text{l.}$ of cyclohexene.

Using the calculations above a curve was plotted of the concentrations of trans-1,3-pentadiene vs. the ratio of the area under the pentadiene peak over the area under the cyclohexene peak or

$$\% \text{ 1,3-pentadiene} = \frac{\text{area under pentadiene peak}}{\text{area under cyclohexene peak}}$$

This was done for five concentrations of 1,3-pentadiene, the resulting curve is shown in Figure 5. From this curve and the areas of the 1,3-pentadiene and cyclohexene peaks it is possible to determine the concentration or yield of 1,3-pentadiene in the volatile mixture and the cis to trans isomer ratio.

To make sure that the distillation of the 1,3-pentadiene was quantitative the chromatogram of the residue was taken. In all cases the remaining 1,3-pentadiene constituted less than 1 mole per cent of the theoretical yield.

Since trans-1,3-pentadiene was used for the calibration a possible error might arise if the detector response differed for the cis isomer. Therefore a 20 mole per cent solution of the cis-1,3-pentadiene was made up and analyzed using the calibration curve based on trans-1,3-pentadiene. The calculated amount of cis isomer was 19.8 per cent which is an error of 1 per cent. Therefore it was assumed that the detector response was the same for both isomers and the one curve was used to calculate the yields of both cis and trans-1,3-pentadiene.

For the quantitative analysis of the 2-pentene system the isomer ratios were calculated both by area and peak height. The two methods agreed within 2 per cent.

Qualitative Analysis

The reproduction of the chromatogram of the product mixture resulting from the reaction of allylidenetriphenylphosphorane and acetaldehyde under standard conditions is shown in Figure 6. The peaks are numbered from (1) through (11). Peaks (8) (9) (10) and (11) were obtained at approximately 45° C. while peaks (1) through (7) were obtained at 25° C.

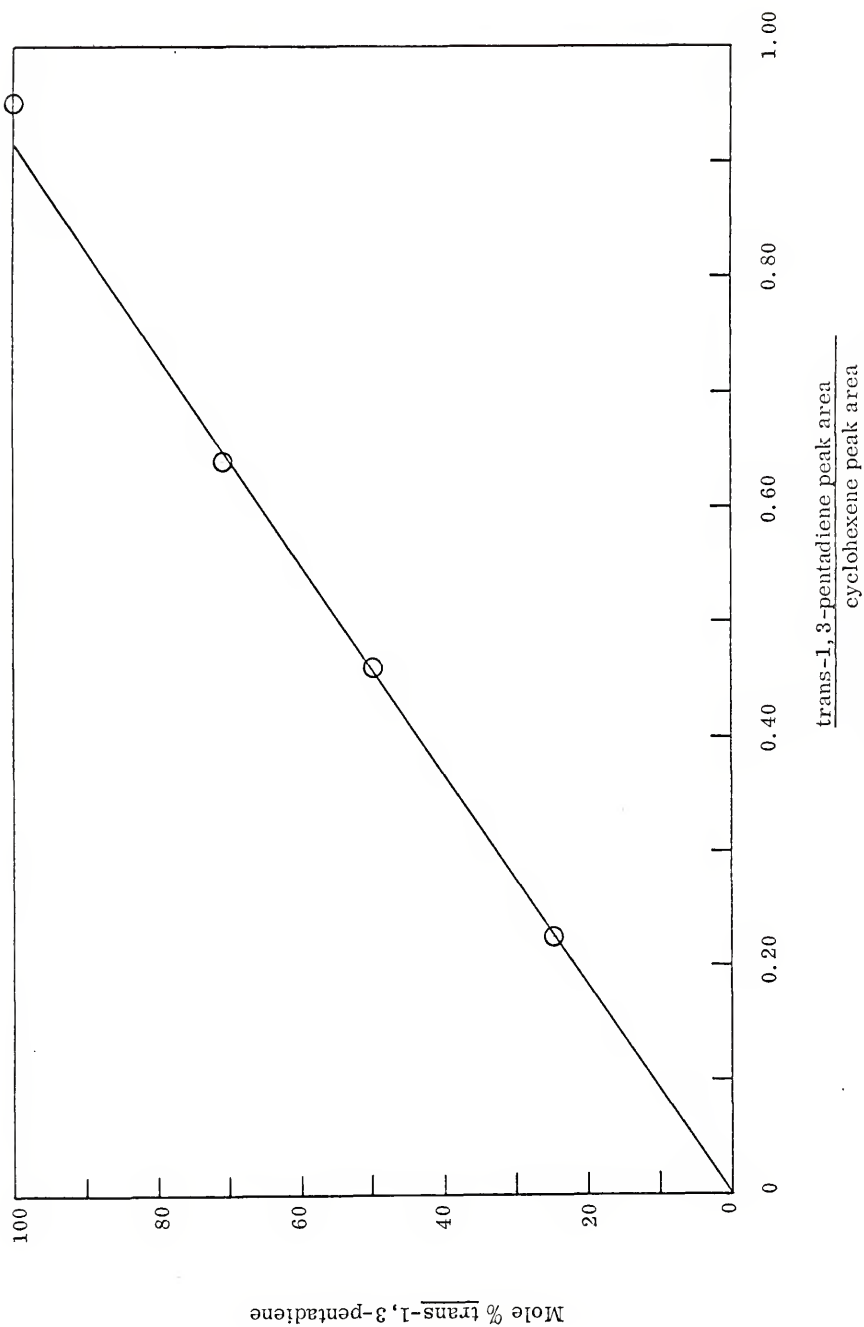


Figure 5. Calibration Curve for trans-1,3-pentadiene

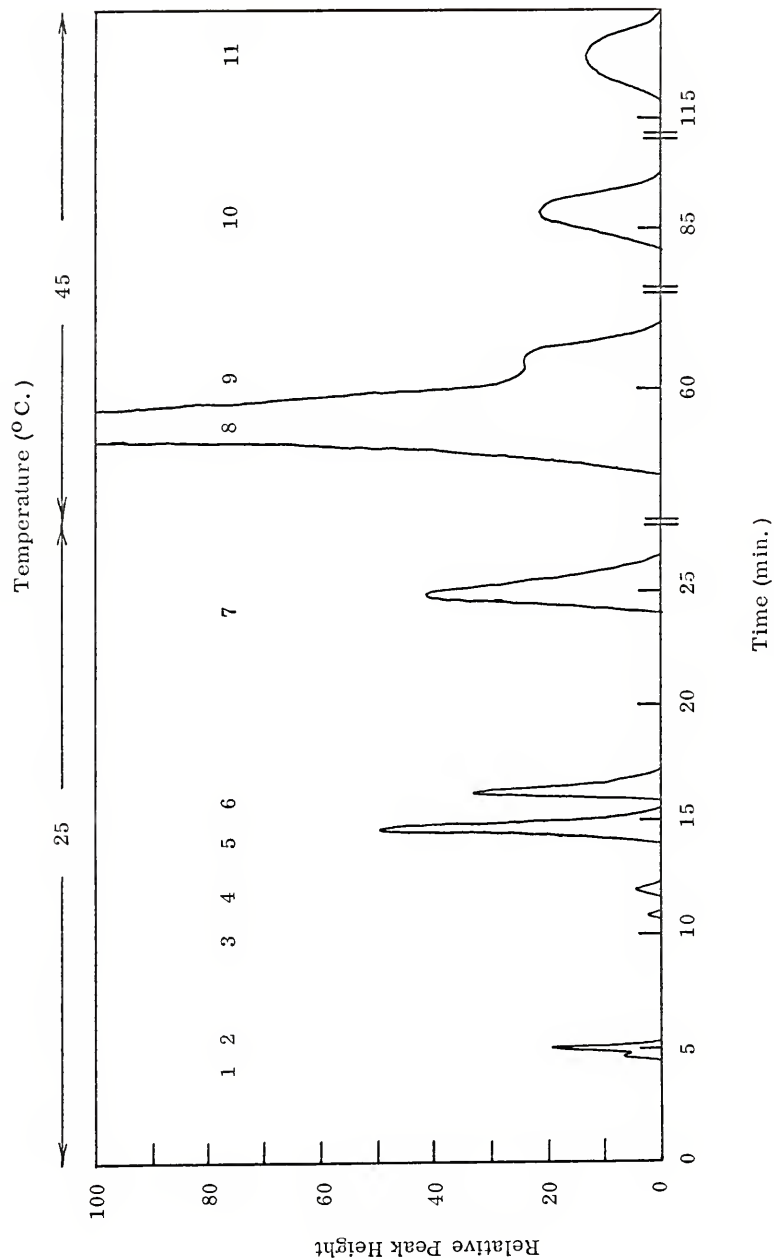


Figure 6. Chromatogram of Reaction Products

Peaks (10) and (11) were cis and trans decalin. They showed increased peak height on the addition of a few drops of pure decalin (mixed isomers) to the product mixture. Peaks (8) and (9) are tetrahydrofuran and benzene respectively which were identified by the above procedure. Peak (7) is cyclohexene the internal standard. Peak (6) is cis-1,3-pentadiene and peak (5) is trans-1,3-pentadiene identified by the addition of authentic samples of the pure isomers to the product mixture as above. Peaks (3) and (4) are trans and cis-2-hexene respectively also identified by the addition of authentic samples of the pure isomers to the mixture. Peak (8) is n-butane identified by the enhanced peak height observed on addition of a THF solution of n-butane prepared by the hydrolysis of n-butyl magnesium bromide. Peak (1) is propene identified by the addition of bromine to the product mixture and then noting the propylene bromide peak enhancement following the addition of known propylene bromide.

Precision of Chromatographic Analysis

A measure of the precision of the determination of the cis:trans isomer ratio may be obtained by taking the average of the average deviations for the duplicate runs. This is ± 0.7 with the largest average deviation being ± 1.7 .

The precision of the yield determination as given by taking the average of the average deviations for the duplicate runs is ± 2.0 with the largest average deviation being ± 5.0 .

A summary of the infrared absorption bands for the phosphonium salts used in this research is shown in Table 12. As a means of identifying individual phosphonium salts, infrared is impracticable. However the alkyl group of the lower

TABLE 12
INFRARED ABSORPTIONS OF PHOSPHONIUM SALTS

| Salt | |
|--------------------------------------|---|
| Methyltriphenylphosphonium chloride | 1979 w, 1903 w, 1820 w, 1780 w, 1671 w, 1620 w, 1595 m-s, 1490 m-s, 1443 s, 1420 m-s, 1400 m, 1339 m, 1318 m, 1306 sh, 1118 s, 998 m-s, 900 s cm ⁻¹ |
| Methyltriphenylphosphonium bromide | 1978 w, 1902 w, 1821 w, 1779 w, 1671 w, 1620 w, 1594 m-s, 1489 m-s, 1442 s, 1419 m-s, 1394 m, 1338 m, 1316 m, 1304 w-m, 1116 s, 998 m-s, 899 s cm ⁻¹ |
| Methyltriphenylphosphonium iodide | 1976 w, 1902 w, 1821 w, 1779 w, 1671 w, 1620 w, 1593 m-s, 1488 m-s, 1441 s, 1418 m-s, 1394 m, 1337 m, 1318 m, 1302 w-m, 1116 s, 998 m-s, 896 s cm ⁻¹ |
| Ethyltriphenylphosphonium chloride | 1974 w, 1901 w, 1820 w, 1778 w, 1590 m, 1480 m-s, 1437 s, 1420 m-s, 1388 m, 1332 m, 1312 m, 1108 s, 994 m-s cm ⁻¹ |
| Ethyltriphenylphosphonium bromide | 1974 w, 1908 w, 1821 w, 1777 w, 1665 w, 1591 m, 1485 m-s, 1439 s, 1420 m-s, 1390 m, 1333 m, 1313 m, 1110 s, 995 m-s cm ⁻¹ |
| Ethyltriphenylphosphonium iodide | 1978 w, 1907 w, 1824 w, 1780 w, 1672 w, 1594 m-s, 1490 m-s, 1442 s, 1425 m-s, 1389 m, 1317 m, 1113 s, 998 s, cm ⁻¹ |
| Allyltriphenylphosphonium chloride | 1979 w, 1903 w, 1821 w, 1778 w, 1639 m, 1613 m-s, 1592 m, 1487 m-s, 1439 s, 1422 m-s, 1390 m, 1334 w-m, 1313 m-s, 1109 s, 997 m-s, 960 m cm ⁻¹ |
| Allyltriphenylphosphonium bromide | 1981 w, 1906 w, 1820 w, 1778 w, 1616 w, 1593 m, 1487 m, 1442 s, 1423 m-s, 1394 m, 1335 w-m, 1315 w-m, 1113 s, 998 m-s, 990 sh cm ⁻¹ |
| Allyltriphenylphosphonium iodide | 1979 w, 1899 w, 1820 w, 1776 w, 1635 w, 1611 w, 1590 m, 1483 m, 1438 s, 1420 m-s, 1391 m, 1333 w-m, 1312 w-m, 1108 s, 994 m-s, 986 sh cm ⁻¹ |
| n-Propyltriphenylphosphonium bromide | 1978 w, 1912 w, 1822 w, 1781 w, 1673 w, 1590 m-s, 1484 m-s, 1463 m, 1438 s, 1334 m, 1313 m, 1110 s, 1076 m-s, 994 m-s cm ⁻¹ |

alkyltriphenylphosphonium salts may be identified by careful analysis of the spectrum.

The methyltriphenylphosphonium salts all appear to have a characteristic strong absorption at $895\text{--}900\text{ cm}^{-1}$ which is missing in the ethyl, allyl and propyl salts.

The allyltriphenylphosphonium salts have the double bond stretching frequency at approximately $1635\text{--}1640\text{ cm}^{-1}$ through which they may be identified.

The ethyl and propyltriphenylphosphonium salts have no special absorption bands by which they may be identified.

The infrared spectra were taken on the Beckman 1R 10 as 0.25 M solutions in chloroform in a 0.175 mm cell. The reported range is from $2000\text{ to }800\text{ cm}^{-1}$.

CHAPTER IV

SUMMARY

The purpose of this research was to investigate factors influencing the stereochemistry of the Wittig reaction. Based on this work the following conclusions may be drawn: (1) There is no observable solvent effect on the stereochemistry of the reaction under the experimental conditions used, although these observations are contrary to the results reported by other investigations; (2) Reaction temperature has no effect on the stereochemistry of the reaction although it has a considerable effect on the yield of product; (3) Even though the reaction is extremely fast at low temperature, reaction time does not affect the stereochemistry of the reaction; (4) The relative concentration of reactants, contrary to the reports of other investigators, has no effect on the stereochemistry of the reaction, although by proper choice of concentrations, high yields of products can be obtained; (5) The nature of the substituents, particularly those on the ylide, has a profound effect on the stereochemical outcome of the reaction; (6) There appears to be either a cation or an anion effect influencing both the ylide and the stereochemistry of the system studied, however, the nature of this effect is too complex to explain with the existing data; and (7) No 1,4-addition of the methylene ylide occurred with crotonaldehyde. A proposal to explain the observations concerned with substituent effects is offered.

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BIOGRAPHICAL SKETCH

Jerome Thomas Kresse was born December 29, 1931, at Buffalo, New York. He obtained his elementary and secondary education in Buffalo graduating from Buffalo Technical High School in 1949. He attended the University of Buffalo from 1949 until 1953. After spending two years in the United States Army he worked for 18 months as a technician with the Silicone's Division of Union Carbide Corporation in Tonawanda, New York. In April 1957 he entered Michigan State University and received the degree of Bachelor of Science in Chemistry in June 1958. He entered the Graduate School of the University of Florida in September 1958.

The author is a member of Alpha Chi Sigma, Professional Chemistry Fraternity and the American Chemical Society. He is married to the former Joan Margaret Schmid and is the father of two children, Jennifer Ann and Michael Jerome.

This dissertation was prepared under the direction of the chairman of the candidate's supervisory committee and has been approved by all members of that committee. It was submitted to the Dean of the College of Arts and Sciences and to the Graduate Council, and was approved as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December 18, 1965

Stephen Jones
Dean, College of Arts and Sciences

Dean, Graduate School

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